Sponsor's Executive Summary

VertiFlex® Superion® Interspinous Spacer

P140004

Orthopaedic and Rehabilitation Devices Panel of the Medical Devices Advisory Committee

February 20, 2015

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1. INTRODUCTION

The subject of this Executive Summary is the **VertiFlex® Superion® Interspinous Spacer** (Superion® device, or Superion® implant) premarket approval (PMA) application, P140004. The Superion® implant is designed for the treatment of symptoms of neurogenic intermittent claudication secondary to moderate spinal stenosis.

The Office of Device Evaluation (ODE) in the Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) requested review of this PMA by the Orthopedic and Rehabilitation Devices Advisory Panel of the Medical Devices Advisory Committee. Specifically, ODE requested a focused review by the Advisory Panel regarding radiographic observations (i.e., spinous process fractures, migrations, dislodgements).

This Executive Summary outlines the clinical study data presented in support of the PMA application for the Superion® Interspinous Spacer. In brief, a prospective, randomized, multi-center, concurrently controlled clinical study was conducted to compare the Superion® device to the control, X-STOP® device for the treatment of symptoms of neurogenic intermittent claudication secondary to moderate lumbar spinal stenosis, executed under FDA oversight with an approved Investigational Device Exemption (IDE). From the patients who met eligibility requirements, 28 non-randomized patients were assigned to the Superion® "training" cohort, while 391 patients were assigned to the modified Intent-to-Treat (mITT) cohort. Of these patients, 190 were randomized to the Superion® arm and 201 to the X-STOP® arm. Patients had follow up through 24 months for the primary endpoint, with additional data collected at annual time points thereafter. The clinical data demonstrate that the Superion® device was statistically non-inferior to the X-STOP® device in a composite endpoint that combines clinical, safety, and radiographic outcomes.

Additional information is provided in this Executive Summary to compare the results of the Superion® IDE to the clinical study used in support of the X-STOP® premarket approval (P040001), as well as other reports in the clinical literature. Of note, the original X-STOP® study did not utilize a standardized radiographic review from an independent radiologist for all patients, as was performed in the Superion® IDE.

Further, this Executive Summary discusses in depth the radiographic observations noted in the Superion® IDE, specifically the incidence of spinous process fractures in the Superion® and X-STOP® groups, and the incidence of device migration and dislodgement in the X-STOP® group. Importantly, these phenomena were primarily noted as part of the independent radiographic review, and patients were largely asymptomatic at, and following time of incidence. An analysis of the underlying causality of these radiographic observations is presented, as well as the relation to clinical outcomes in patients having these observations.

The Executive Summary concludes with a discussion of the benefit to risk comparison for the Superion® device when used to treat symptoms of neurogenic intermittent claudication secondary to moderate lumbar spinal stenosis.

2. SUMMARY

The Superion® Interspinous Spacer (Superion® device or Superion® implant) is a spinal implant designed for the treatment of symptoms of neurogenic intermittent claudication secondary to moderate lumbar spinal stenosis and is implanted by minimally-invasive methods through a cannula. The implant provides an indirect decompression of spinal nerves and functions by serving as a spinal extension blocker. The Superion® device was designed to treat a similar patient population as the approved and commercially-available X-STOP® Interspinous Process Device.

Study Design
A prospective, randomized, multi-center, concurrently controlled clinical study was conducted to compare the Superion® device to the control, X-STOP® device. A total of 470 patients were enrolled in the study, and 51 patients were post-consent screen failures prior to treatment. From the patients who met eligibility criteria, 28 non-randomized patients were assigned to the Superion® "training" cohort, while 391 patients were assigned to the randomized Intent-to-Treat (mITT) cohort. Of these patients, 190 were randomized to the Superion® arm and 201 to the X-STOP® arm.

Patients had follow up examinations at discharge, 6 weeks, 3 months, 6 months, 12 months, 18 months, and 24 months, with annual follow-up visits thereafter.

The primary endpoint of the investigation was a robust composite that included effectiveness, safety, and risk-benefit criteria. Individual patient success required that a patient meet all of the following criteria at 24 month follow up:

- Clinically significant improvement in outcomes compared to baseline, as determined by meeting the criterion for at least two of three domains of ZCQ
    - o $\geq$ 0.5 point improvement in physical function
    - o $\geq$ 0.5 point improvement in symptom severity
    - o Score of $\leq$ 2.5 points on patient satisfaction domain
- No re-operations, removals, revisions, or supplemental fixation at the index level(s)
- No major implant or procedure related complications
    - o No dislodgement, migration, or deformation
    - o New or persistent worsened neurological deficit at the index level
    - o Spinous process fractures
    - o Deep infection, death, or other permanent device attributed disability
- No clinically significant confounding treatments:
    - o No epidural injections or nerve block procedures at index level, spinal cord stimulators or rhizotomies

In addition, a number of secondary outcomes were measured, including clinically significant decreases in leg pain and back pain (measured by $\geq$20mm decrease in Visual Analog Scale [VAS]), maintenance or improvement of SF-12, and clinically significant decrease (defined as $\geq$15 point decrease vs. baseline) in Oswestry Disability Index (ODI). Radiographic assessments were also performed in the Superion® and X-STOP® groups by an independent radiographic core lab to determine qualitative radiographic measures (e.g., device migration or dislodgement, spinous process fracture) and quantitative radiographic measures (e.g., range of motion, disc angle, foraminal height).

Clinical Outcomes

The Superion® cohort had an excellent follow-up rate of 97.3% and the X-STOP® cohort had a follow-up rate of 94.9% through 24 months. Further, for patients theoretically due for 36 month follow-up, the Superion® cohort had a follow-up rate of 90.2% and the X-STOP® cohort had a follow-up rate of 91.4%.

As demonstrated in Table 1, non-inferiority of the Superion® device was established for the primary endpoint by achieving a Bayesian Posterior Probability > 0.958 (as described in the statistical analysis plan), in the modified intent-to-treat cohort. This cohort included all patients with an anesthesia start time in the Superion® trial. Further, the demonstration of non-inferiority in the per protocol cohort provides confirmation of the non-inferiority result of the Superion® trial and demonstrates the robustness of the overall statistical determination.

Table 1: Superion® and X-STOP® Descriptive Comparisons of the Percentages of Patients Achieving the Primary Overall Success Efficacy Criterion[1] All Evaluated

	Number and Percentage Achieving Month 24 Overall Success						Posterior Probability of Non-Inferiority[1]
	Superion®			X-STOP®			
Analysis Cohort	**N**	**n**	**%**	**N**	**n**	**%**	
mITT	183	95	52.7%	187	93	50.2%	0.9927
Per Protocol	173	92	53.2%	178	88	49.4%	0.9944

[1]As described in the SAP for the mITT cohort, missing data for the posterior probability was handled using Bayesian multiple imputation methodologies. The %'s, as well as the posterior probability reported for the Bayesian multiple imputation (MI) are based on the mean over 5000 multiple imputations. The (SD's) over multiple imputations for these estimates were 52.7% (0.6%), 50.2% (0.9%), and 0.9927 (0.0045), respectively. The reported N and n values for this row reflect only the numbers of patients with complete Month 24 CCS. All 190 Superion® and 201 X-STOP® patients were included in the primary analysis of the mITT cohort using Bayesian multiple imputation, whereas all patients with missing primary endpoint data at 24 months were excluded from the Per Protocol cohort.

Patients in the Superion® group exhibited a similar success proportion with all secondary endpoints when compared to the X-STOP® group (Table 2). In addition, radiographic analysis of the Superion® and X-STOP® devices at 24 months post-op showed no disassembly or device collapse. Quantitative and qualitative radiographic data demonstrates both devices block extension.

Table 2: Secondary Endpoints at 24 Month Follow-Up in Superion® Clinical Trial

Outcome Measure	Superion® n/N (%)	X-STOP® n/N (%)	p-value[1]
ODI: ≥15 point decrease	83/131 (63.4%)	89/133 (66.9%)	0.606
VAS Back: ≥20mm decrease	88/131 (67.2%)	91/133 (68.4%)	0.895
VAS Leg (Worse): ≥20mm decrease	99/131 (75.6%)	103/133 (77.4%)	0.772
SF-12 Physical Function: Maintenance or Improvement	103/128 (80.5%)	119/133 (89.5%)	0.055
SF-12 Mental Health: Maintenance or Improvement	77/128 (60.2%)	89/133 (66.9%)	0.303

[1]Fisher's Exact Test

Radiographic Observations

As a component of the primary endpoint, patients with spinous process fractures, migrations, and dislodgements (measured through independent radiographic review to mitigate bias) were considered study failures at 24 months. The incidences of these radiographic observations are shown in Table 3.

Table 3: Subjects with Radiographic Observations in the Superion® IDE

Radiographic Observation	Superion® (n=190)		X-STOP® (n=201)	
	n	%	n	%
Spinous Process Fracture (any time)	31	16.3%	17	8.5%
Spinous Process Fracture (non-healed at 24 months)	21	11.1%	10	5.0%
Device Migration (>5mm)	0	0.0%	16	8.0%
Device Dislodgement	0	0.0%	20	10.0%
Any Radiographic Observation (any time)	31	16.3%	34*	16.9%
Any Radiographic Observation (24 months)	21	11.1%	28	13.9%

*Significant overlap was present in X-STOP® subjects having spinous process fractures, device migration, and device dislodgement.

While the incidence of spinous process fractures was higher in the Superion® group, the overall rate of radiographic observation was similar in both treatment groups (16.3% of Superion® vs. 16.9% of X-STOP®, p=0.690). The clinical sequelae associated with these events were different between spinous process fractures and migrations/dislodgements. The severity and magnitude of clinical outcomes in these patients is presented in Section 11.

The FDA has expressed concerns regarding the rate of spinous process fractures, the impact or significance of the clinical sequelae of spinous process fractures, and the suitability of comparing spinous process fractures to migrations/dislodgements. In order to have an objective endpoint, both spinous process fractures and device migrations/dislodgements were considered primary endpoint failures at 24 months. These endpoints were designed *a priori* and continue to provide not only a good assessment of safety and effectiveness, but by considering these observations as failures regardless of clinical outcome, represents a scientific method of evaluating risk/benefit of the Superion® device.

Based on the PMA and study outcomes, while the rate of spinous process fractures was higher in the Superion group, VertiFlex has demonstrated that these observations are not a clinical concern based upon clinical outcomes (ZCQ, ODI, VAS Back and VAS Leg), as subjects incurring spinous process fractures were, in large part, asymptomatic. On the other hand, device migrations/dislodgements have been shown to have some adverse clinical sequelae in the form of increased back pain among these patients, as measured by VAS. Clinical outcomes of both of these radiographic scenarios are provided in this document. Lastly, possible causes of spinous process fractures were investigated and the clinically relevant ones are presented in this document, as are methods for mitigating the overall risk of spinous process fracture.

Overall, the Superion® device demonstrated that it is safe and effective compared to the X-STOP® device for the treatment of moderate spinal stenosis. The study has a combined follow-up rate of 94.6% and demonstrated a 0.9927 posterior probability of non-inferiority per the approved statistical plan, which exceeds the 0.958 posterior probability defining success. The 50.2% Superion® success rate was determined using a complex and thorough composite endpoint that included clinical success, lack of additional treatments for stenosis, and lack of radiographic observations at 24 months postoperatively. The Superion® device also demonstrated a positive benefit/risk ratio by not only demonstrating non-inferiority at 24 months with pain and function measurements comparable to the control device, clinical improvement in all pain and function measurements out to 36 months, but also the complete absence of migrations and dislodgements. Furthermore, the Superion® device demonstrated improved results at 3 years follow-up compared to X-STOP® device. Importantly, this suggests continued and durable effectiveness of the Superion® device over the longer term.

3. BACKGROUND INFORMATION

3.1. Applicant's Name and Address

VertiFlex®, Incorporated
1351 Calle Avanzado, Suite 100
San Clemente, CA 92673

3.2. Device Description

The Superion® Interspinous Spacer (Superion® device) is a spinal implant designed for the treatment of lumbar spinal stenosis (Figure 1). The device is implanted by minimally-invasive methods through a cannula using manual instrumentation of proprietary design supplied by VertiFlex®.

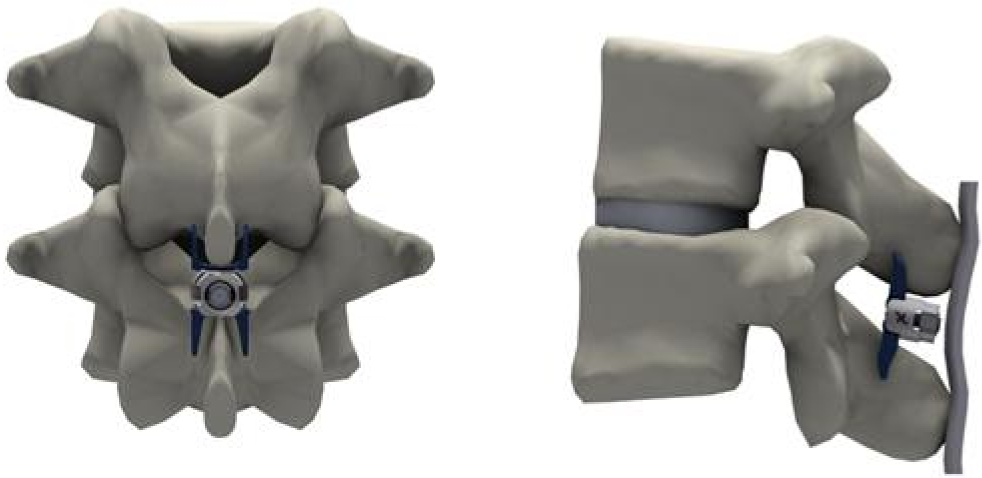


Figure 1: Superion® InterSpinous Spacer in situ

The VertiFlex® Superion® device can generally be described in two (2) "states": Un-deployed (or closed), and deployed (or open). The implant is supplied in the un-deployed, or closed state, and it is in this form that it is passed through a delivery cannula inserted at midline to the selected implantation site. Once delivered to, and located in, the interspinous space between the spinous processes at the selected level, the Superion® implant is deployed to open the superior and inferior cam lobes. In doing so, these cam lobes rotate 90° to engage the lateral aspects of the superior and inferior spinous processes posterior to the lamina. Figure 2 provides views of the implant as it transitions from the closed to open (or deployed) configuration.

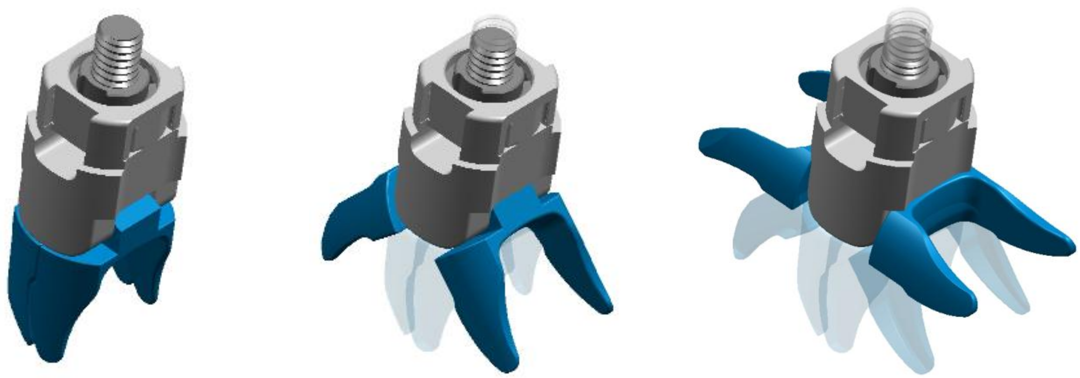
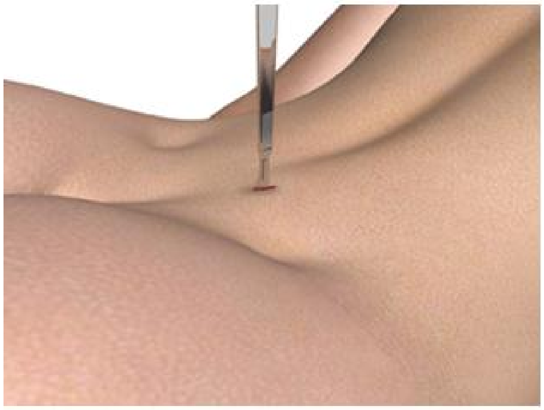
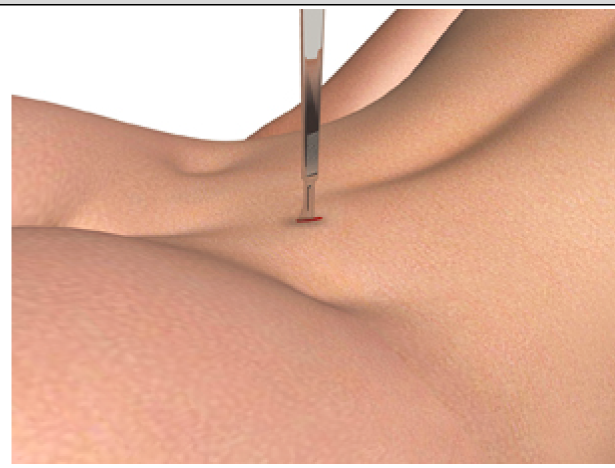
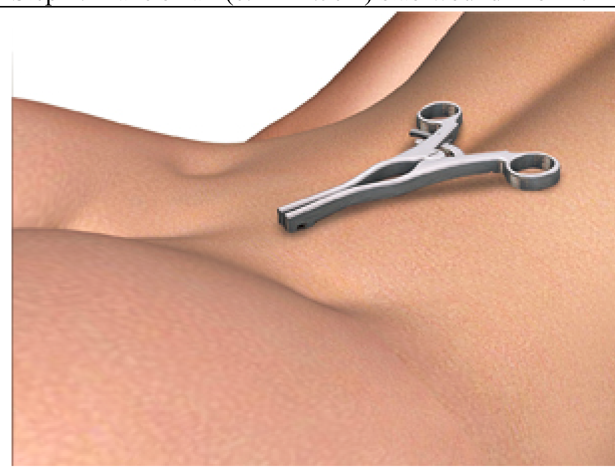
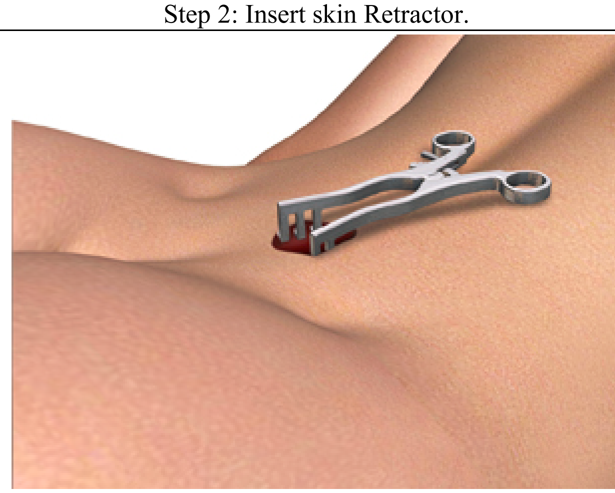
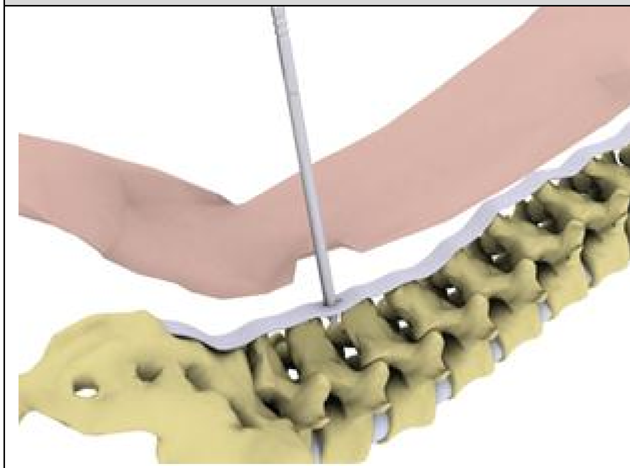
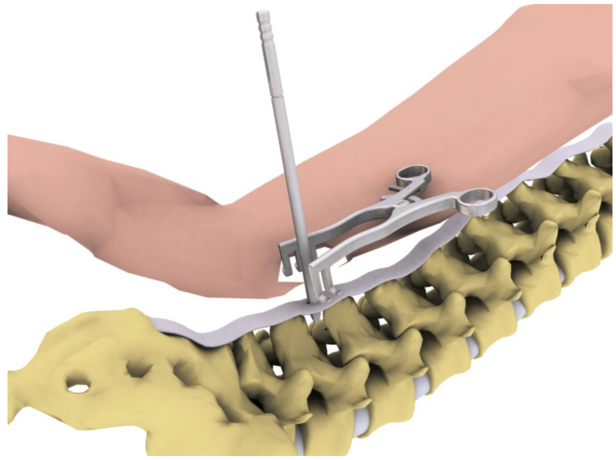
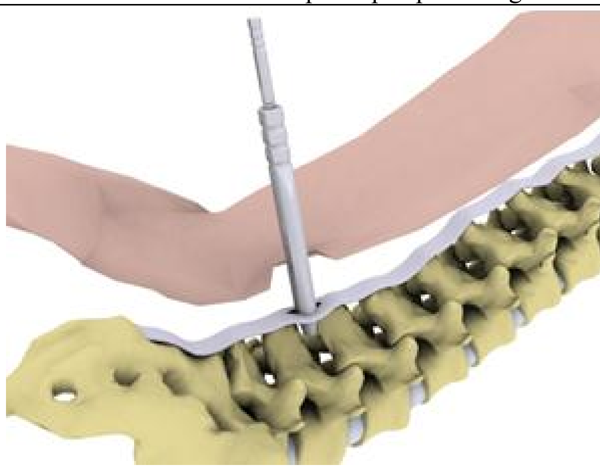
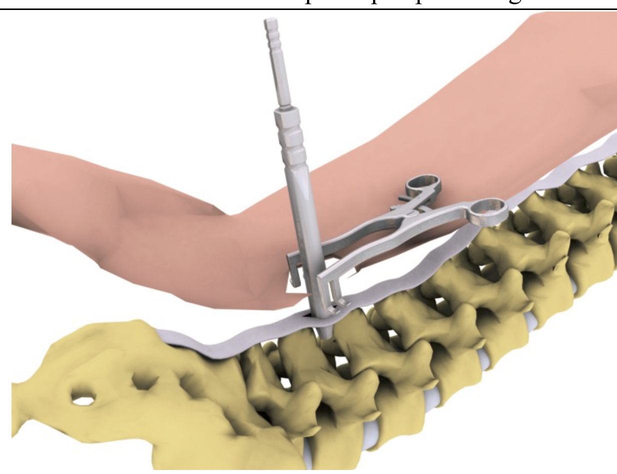
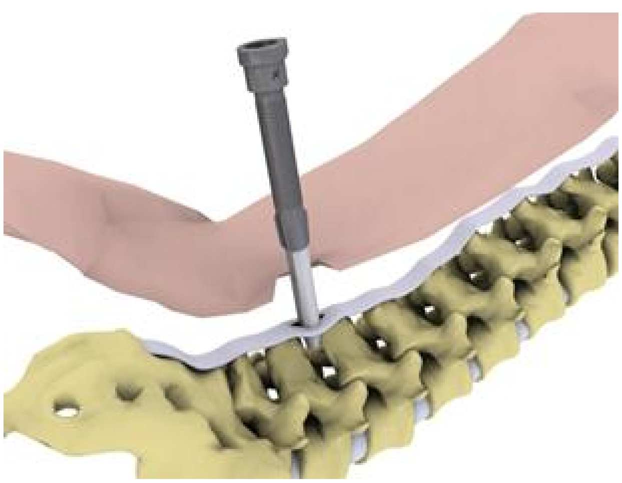


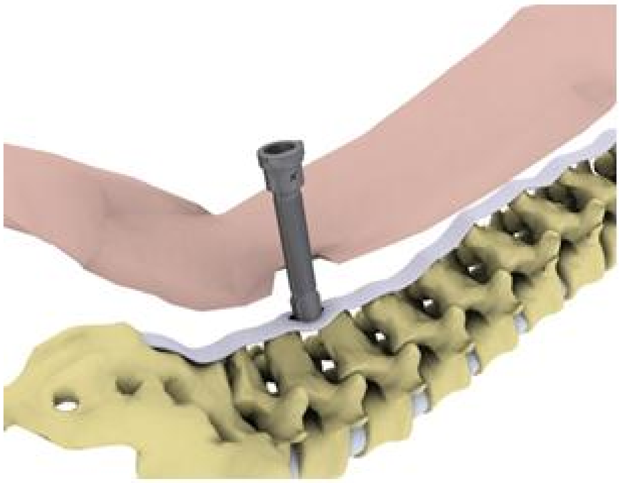
Figure 2: Superion® Device in Closed and Extended Position

The device may be placed under general, or under local (e.g., conscious sedation) anesthesia. Depictions of individual steps of the Superion® implantation procedure are included in Table 4, showing both the purely percutaneous (fluroscopically-guided) and "mini-open" approaches.

Table 4: Surgical Technique Approaches for Superion® Device

Percutaneous (Fluoroscopic) Approach	Mini-Open Approach
 Step 1: Make small (c. 1 – 1.5cm) stab wound in skin	 Step 1: Make small (c. 1 – 1.5cm) stab wound in skin.
(No equivalent step, visualization achieved with fluoroscopic guidance)	 Step 2: Insert skin Retractor.
(No equivalent step, visualization achieved with fluoroscopic guidance)	 Step 3: Open skin Retractor sufficiently to visualize dorsal aspect of supraspinous ligament.

Percutaneous (Fluoroscopic) Approach	Mini-Open Approach
 Step 4: Under fluoroscopic guidance, position Dilator 1 at midline and advance to split supraspinous ligament.	 Step 4: Under direct visualization, position Dilator 1 at midline and advance to split supraspinous ligament.
 Step 5: Advance Dilator 2 over Dilator 1.	 Step 5: Advance Dilator 2 over Dilator 1.
 Step 6: Advance Cannula over Dilator 2.	 Step 6: Advance Cannula over Dilator 2.

<table>
<tr><th>Percutaneous (Fluoroscopic) Approach</th><th>Mini-Open Approach</th></tr>
<tr><td>
Step 7: Remove Dilators to leave Cannula positioned between spinous processes.</td><td>
Step 7: Remove Dilators to leave Cannula positioned between spinous processes.</td></tr>
</table>

Initially, the patient is placed with the spine in a slightly flexed position to permit easier placement of the cannula. A percutaneous or mini-open approach is used for incision and placement of the cannula via sequential dilation. The supraspinous ligament is separated parallel to the collagen fiber orientation to allow access to the interspinous space for the cannula. Once the cannula is in place, a sizing tool is utilized to determine the proper device size. The Superion® implant is then inserted under fluoroscopic guidance through the cannula and between adjacent vertebral spinous processes at one level, or at two contiguous levels if necessary. Following insertion, the supraspinous ligament may be closed with a suture. The rigid implant serves thereafter to maintain the desired amount of distraction between the spinous processes while still preserving motion. This maintains the intervertebral space and prevents narrowing of the canal by limiting extension at that level.

The Superion® implant is designed to relieve or mitigate symptoms of intermittent neurogenic claudication (primarily leg, buttock, or groin pain and/or weakness), in those individuals who have moderate lumbar spinal stenosis (LSS), and whose symptoms are relieved in flexion. Such symptoms are typically exacerbated when the patient is standing or walking, such that the lumbar spine is in mild extension. Extension serves to further narrow the stenosed nerve channels (i.e., neural foramen and/or spinal canal), thereby compressing the neural elements and triggering or worsening the symptoms, and so, restricting extension at the symptomatic level(s) is a key objective of the device.

Placement of the Superion® Interspinous Spacer between two adjacent spinous processes is intended to limit compression at the treated level by blocking extension of the affected spinal segment. By preventing or limiting the compression of neural elements in extension, the spacer reduces the symptoms of neurogenic intermittent claudication.

4. INDICATIONS FOR USE

The Superion® InterSpinous Spacer (the Superion® ISS) is intended to treat skeletally mature patients suffering from pain, numbness, and/or cramping in the legs (neurogenic intermittent claudication) secondary to a diagnosis of moderate lumbar spinal stenosis, with or without Grade 1 spondylolisthesis, confirmed by X-ray, MRI and/or CT evidence of thickened ligamentum flavum, narrowed lateral recess, and/or central canal or foraminal narrowing. The Superion® ISS is indicated for those patients with impaired physical function who experience relief in flexion from symptoms of leg/buttock/groin pain, numbness, and/or cramping, with or without back pain. The Superion® ISS may be implanted at one or two adjacent lumbar levels in patients in whom treatment is indicated at no more than two levels, from L1 to L5.

5. CONTRAINDICATIONS

The Superion® Interspinous Spacer is contraindicated in patients with:

- an allergy to titanium or titanium alloy;
- spinal anatomy or disease that would prevent implantation of the device or cause the device to be unstable in situ, such as:
- significant instability of the lumbar spine, e.g., isthmic spondylolisthesis or degenerative spondylolisthesis greater than grade 1.0 (on a scale of 1 to 4);
- an ankylosed segment at the affected level(s);
- acute fracture of the spinous process, pars interarticularis, or laminae fracture (unilateral or bilateral);
- significant scoliosis (Cobb angle >10 degrees);
- Cauda equina syndrome defined as neural compression causing neurogenic bladder or bowel dysfunction;
- diagnosis of severe osteoporosis, defined as bone mineral density (from DEXA scan or equivalent method) in the spine or hip that is more than 2.5 S.D. below the mean of adult normals in the presence of one or more fragility fractures;
- active systemic infection, or infection localized to the site of implantation.

6. REGULATORY & MARKETING HISTORY

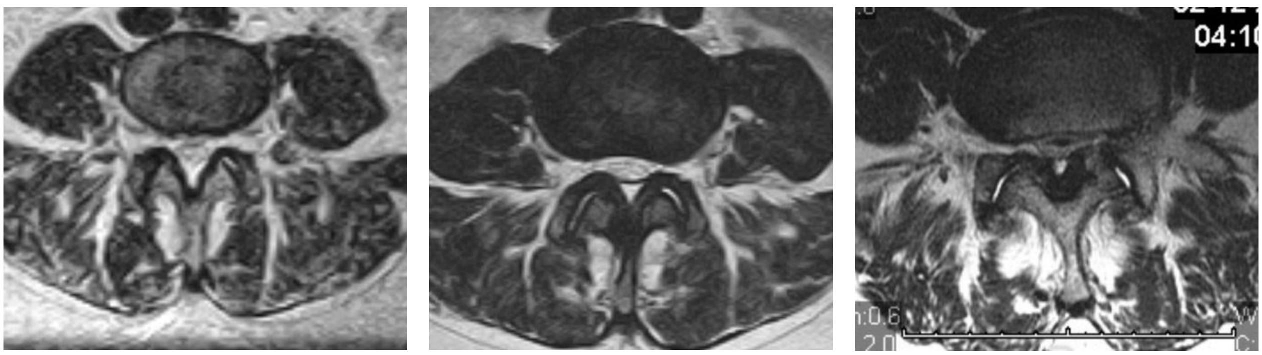
The Superion® InterSpinous Spacer was granted CE Mark in January 2007, and has been commercially available in markets outside the U.S. since that time, having been used over 2,000 times. A listing of countries in which the device is or has been commercially available is provided below. The Superion® device has not been withdrawn from commercial distribution in any of these markets.

- Israel
- South Africa
- United Kingdom
- Italy
- Spain
- Mexico
- Germany
- Netherlands

7. UNDERLYING DISEASE STATE

Spinal stenosis is defined as the narrowing of the central spinal canal, nerve root canals, and/or intervertebral foramina that leads to compression of the exiting or traversing spinal nerve roots[1]. Symptoms most often occur in patients > 50 years of age, and may therefore have a significant negative impact on the elderly population. Data from the Framingham Heart Study indicates that 1% of men and 1.5% of women already had evidence of stenosis at baseline (mean age of 54), increasing to 11% of men and 25% of women over the 25-year follow-up period[2].

A diagnosis of spinal stenosis can have varying degrees of severity, as well as other concomitant conditions. Figure 3 provides examples of varying severity of spinal stenosis, as observed radiographically.



(a) (b) (c)

Figure 3: Coronal MRIs Depicting Differing Severity of Central Spinal Stenosis (a) Mild, (b) Moderate, and (c) Severe

At initial presentation, patients may complain of low back pain, buttock pain, leg pain, numbness, tingling, cramping, and/or trochanteric and posterior thigh pain that may radiate to the knee, lateral thigh, calves, and occasionally the feet[3]. In the earlier stages of the disease, these symptoms may be relieved by sitting or lying down and may be exacerbated by walking, especially downhill[4], an occurrence known as intermittent neurogenic claudication. While plain radiographs, three dimensional imaging methods, and other radiographic measurements are useful in confirming the diagnosis of spinal stenosis, a careful clinical history is the necessary means for establishing the diagnosis[5]. In addition to leg/buttock pain, spinal stenosis patients may also complain of debilitating low back pain that is most commonly attributed to facet-based arthrosis, degenerative disc disease (DDD), or muscular strain.

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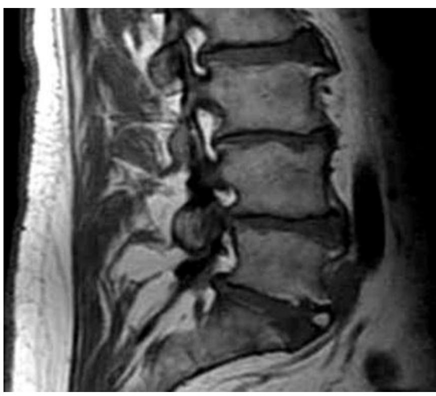
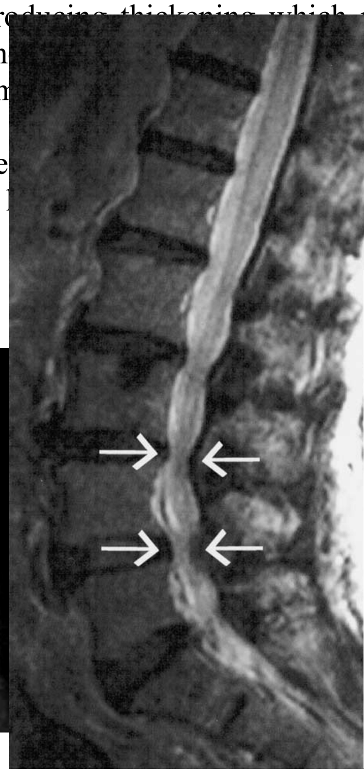
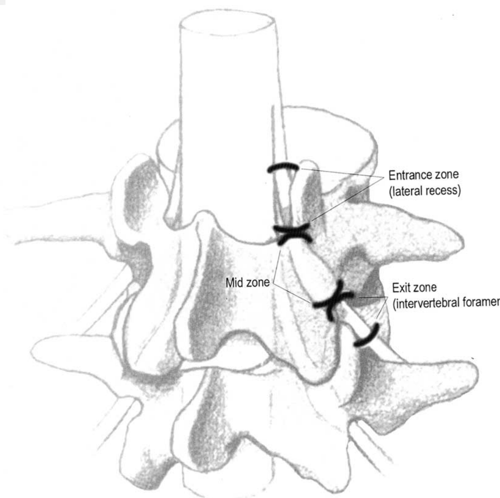
[1] Arnoldi CC, Brodsky AE, Cauchoix J, et al. Lumbar spinal stenosis and nerve root entrapment syndrome. Definition and classification. *Clin Orthop* 1976; 115:4-5.
[2] Treatment of Degenerative Lumbar Spinal Stenosis. Summary, Evidence Report/Technology Assessment: Number 32. AHRQ Publication No. 01-E047, March 2001. Agency for Healthcare Research and Quality, Rockville, MD. Available at http://www.ahrq.gov/clinic/epcsums/stenosum.htm.
[3] Yong-Hing K, Kirkaldy-Willis WH. The pathophysiology of degenerative disease of the lumbar spine. *Orthop Clin North Am.* 1983;14:501-3.
[4] Delamarter RB, Howard M.: Lumbar spinal stenosis. Rehabilitation of the Spine, Science and Practice. Editors Hochschular S, Cotler H., Guyer R, Chapter 37, pp. 443-456, Mosby, 1993.
[5] Deyo RA, Rainville J, Kent DL. What can the history of physical examination tell us about low back pain? *JAMA* 1992;268:760-5.

While spinal stenosis can be congenital, it is most often the result of degenerative changes to the spine, typically those observed with aging. Degenerative spinal stenosis typically begins with degenerative changes of the nucleus pulposus portion of the intervertebral disc. As the disc degenerates and narrows, the vertebrae become more closely positioned to one another, which may result in ligament laxity and lead to intersegmental instability[6]. These changes can lead to osteophyte formation, which has the effect of temporarily restabilizing the unstable spinal segment. The presence of circumferential osteophytes, together with loss of disc space height, contribute to neural foraminal narrowing. As the degenerative changes progress, the ligamentum flavum shortens and buckles, pr [...] may further reduce canal area and contribute to central spinal sten [...] changes to the facet joints with secondary osteophyte formation n [...] al recess stenosis.

Stenosis can be further classifie [...] l impingement. Figure 4 presents images of foraminal, central, and l [...]







(a) (b) (c)

Figure 4: Types of Stenosis: (a) MRI Depicting Foraminal Stenosis (b) MRI Depicting Central Stenosis[2] (c) Diagram of Lateral Stenosis[8]

The initial diagnosis of spinal stenosis is usually based on patient history and physical examination, typically including a neurological examination. Confirmation of the diagnosis and delineation of both the degree of disease and its etiology may be accomplished by imaging methods such as plain radiograph, CT scan (with or without myelographic contrast), and MRI, and non-imaging tests such as electromyography (EMG)[9]. Many different parameters have been reported for objectively or semi-objectively evaluating the degree of spinal stenosis, most of

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[6] Fast A, Greenbaum M. Degenerative lumbar spinal stenosis. *Phys Med Rehabil St Art Rev* 1995; Oct. 9:673-82.

[7] Yong-Hing K, Kirkaldy-Willis WH. The pathophysiology of degenerative disease of the lumbar spine. *Orthop Clin North Am.* 1983;14:501-3.

[8] Botwin, KP, Gruber RD. Lumbar Spinal Stenosis: Anatomy and Pathogenesis. Phys Med Rehabil of Clin N Am 14 (2003) 1-15

[9] Delamarter RB, Howard M.: Lumbar spinal stenosis. Rehabilitation of the Spine, Science and Practice. Editors Hochschular S, Cotler H., Guyer R, Chapter 37, pp. 443-456, Mosby, 1993.

which evaluate either the anterior to posterior (AP) dimension of the spinal canal, or its cross-sectional area[10].

7.1. Moderate Spinal Stenosis

The severity of spinal stenosis is often the driving factor in the treatment methodology. Severity can range from “mild” stenosis, where tissue impingement on spinal nerves and/or the spinal cord manifest symptoms that are generally are treated successfully with conservative (non-surgical) care, to “severe” stenosis, where significant amounts of impeding bone and ligamentum flavum need to be removed via direct surgical decompression with or without additional mechanical stabilization, to address symptoms. In addition, severe spinal stenosis is often associated with significant spondylolisthesis or retrolisthesis, creating instability in the spine once a decompression surgery is performed that may require stabilization with instrumentation.

It is recognized that spinal stenosis is a progressively degenerative condition that often continues to worsen as patients age. Non-surgical or conservative treatments, while effective in early and milder stages of the disease, may later prove ineffective as the stenosis worsens. Patients that have continued back and leg pain after conservative care has become ineffective are often diagnosed with “moderate” stenosis. These patients have progressed to a point where direct decompression is not yet required to achieve symptom relief, but where non-operative treatments are no longer effective.

Moderate stenosis is diagnosed clinically through patient symptomatology and is confirmed through radiographic criteria. The clinical hallmark of moderate stenosis is persistent leg, buttock, or groin pain, with or without back pain, that is relieved by placing the spine in flexion (e.g., leaning forward or bending over a shopping cart). These patients are generally no longer responsive to varying non-surgical treatments to relieve pain. In order to assess the extent of the pain and impaired function, validated scoring systems such as the Zurich Claudication Questionnaire can be used. In the clinical trial supporting PMA approval of the X-STOP® device, moderate stenosis was further defined, in part, as patients who present with moderately impaired Physical Function (PF) defined as a score of ≥2.0 on the Zurich Claudication Questionnaire. When stenosis reaches a moderate severity and non-surgical care no longer mitigates symptoms, the only way to achieve sufficient pain relief is through surgical means.

Confirmation of moderate spinal stenosis is obtained by radiographic measurements, often defined as 25% to 50% reduction in lateral and/or central foraminal area compared to the adjacent levels. In addition, the patient can exhibit other radiographic evidence of moderate stenosis, including cauda equina compression, nerve root impingement, and hypertrophic facets with canal encroachment.

[10] See, Treatment of Degenerative Lumbar Spinal Stenosis. Summary, Evidence Report/Technology Assessment: Number 32. AHRQ Publication No. 01-E047, March 2001. Agency for Healthcare Research and Quality, Rockville, MD. Available at http://www.ahrq.gov/clinic/epcsums/stenosum.htm.

7.2. Treatment Options

An overall outline of the treatment continuum for spinal stenosis is included in Figure 5. As shown by this figure, treatment options for spinal stenosis generally range from non-invasive, or conservative, treatments for conditions with milder symptoms, to invasive surgical options for moderate to severe stenosis, the latter often compounded by spinal instability. Surgical options range from indirect decompression devices (including both the subject Superion® device and the control X-STOP® device) to decompression procedures, with or without the coflex® device, to fusion procedures with stabilizing instrumentation. Increased surgical complexity and invasiveness is often associated with increased morbidity.

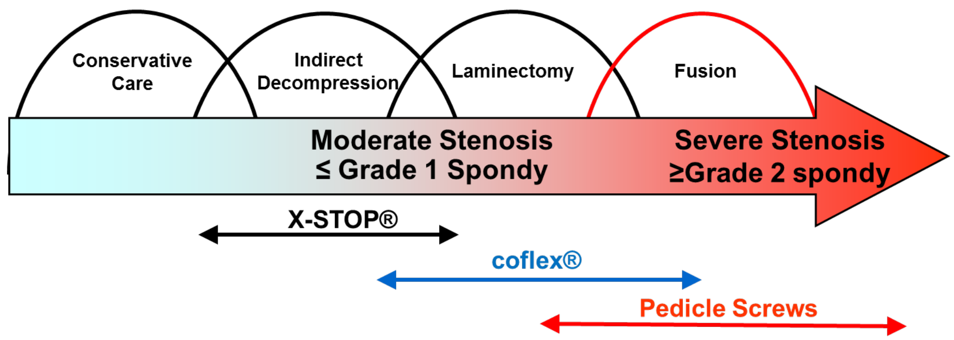

Figure 5: Stenosis Treatment Continuum

7.2.1. Conservative Care

As previously stated, in its early stages, spinal stenosis is primarily treated with physical therapy and other non-invasive methods of symptom management. As outlined in the North American Spine Society (NASS) guidelines for the treatment of spinal stenosis[11], initial treatments for spinal stenosis include modifications to daily living (bed rest, activity modification), bracing, medication (NSAIDs, opiates), and spinal manipulation. Of these, only bracing has demonstrated sufficient evidence of success in the literature, although there is no evidence that results are sustained once the brace is removed. For patients who do not respond to conservative care, an epidural steroid injection at the symptomatic level(s) is generally the next step in the treatment algorithm. NASS guidelines suggest epidural injections to provide short-term (two weeks to six months) symptom relief in patients with neurogenic claudication, although these treatments are still focused on symptom management and not on treating the underlying disease or pathology. If epidural treatment or pain management does not lead to an improved patient outcome, then surgical treatment is outlined as the next step in the care continuum. In patients with symptoms of moderate stenosis, non-surgical care has not been, or is no longer, effective in mitigating the symptoms of lumbar spinal stenosis.

[11] North American Spine Society. Clinical Guidelines for Multidisciplinary Spine Care: Diagnosis and Treatment of Degenerative Lumbar Spinal Stenosis. 2011.

7.2.2. Surgical Treatment

In the setting of lumbar spinal stenosis and degenerative spondylolisthesis recalcitrant to conservative treatment, surgical options have been shown in the recent NIH-funded SPORT trials to produce universally excellent results and superiority over non-operative treatment with results sustained at 4 years. The SPORT trials are Level 1 evidence and reflect the highest quality studies performed to date comparing conservative versus surgical treatment for spinal stenosis[12,13,14,15,16,17]. Depending on the nature of the pathology encountered, there are two types of decompression that can be considered: indirect and direct decompression (with the appropriate stabilization). When considering indirect decompression, the only currently marketed device is the X-STOP® Interspinous Process Distraction Device. The investigational Superion® device is also indicated for the treatment of symptoms secondary to moderate stenosis and operates by the same mechanism. The direct decompression options would consist of laminectomy, laminotomy, foraminotomy, decompression with stabilization with coflex® Interlaminar Technology, or laminectomy with posterior instrumentation and spinal fusion. Most of these options are indicated for moderate to severe spinal stenosis or stenosis in which instability exists.

Indirect Decompression

For those patients that are demonstrating symptoms of neurogenic intermittent claudication secondary to moderate stenosis, the X-STOP® Interspinous Process Distraction Device (IPD®) can also be considered a treatment modality. The X-STOP® IPD® has been approved to provide *indirect* neural decompression (i.e., decompression without surgical removal of soft or bony tissue impinging neural elements) by acting as an extension blocker, thus inhibiting compression of neural elements in extension. In this technique, a direct surgical decompression is not performed, and any neurologic recovery is contingent upon adequate indirect neuroforaminal decompression and restriction of extension (extension blocking). While the procedure does not include direct decompression of the bony or discal elements impinging upon the spinal nerves, the procedure does involve deep dissection and exposure of the lateral aspects of the spinous processes and may also involve removal of some tissue between the spinous processes to permit implant placement. (This is in contrast to the minimally-invasive technique by which the Superion® is placed.) This surgical exposure can lead to morbidity in the form of scar tissue formation which can compromise any future surgical procedures, should they become necessary, and to complications related to the incision size, sites, and extent, such as dural tears or deep infection. Furthermore, and again in contrast to the Superion® device,. Furthermore, the radiographic risk of dislodgement due to the size and dimensions of the X-STOP® implant has

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[12] Birkmeyer NJ. Design of the Spine Patient outcomes Research Trial (SPORT). 2002.

[13] Pearson A. Degenerative spondylolisthesis versus spinal stenosis: does a slip matter? Comparison of baseline characteristics and outcomes (SPORT). 2010.

[14] Tosteson AN. The cost effectiveness of surgical versus nonoperative treatment for lumbar disc herniation over two years: evidence from the Spine Patient Outcomes Research Trial (SPORT). 2008.

[15] Weinstein JN. Surgical versus nonsurgical treatment for lumbar degenerative spondylolisthesis. 2007.

[16] Weinstein JN. Surgical compared with nonoperative treatment for lumbar degenerative spondylolisthesis. four-year results in the Spine Patient Outcomes Research Trial (SPORT) randomized and observational cohorts. 2009.

[17] Weinstein JN. Surgical Versus Nonoperative Treatment for Lumbar Spinal Stenosis Four-Year Results of the Spine Patient Outcomes Research Trial. 2010.

been seen in numerous patients due to the device loading *in situ* and the geometry of the device tines.

Direct Decompression

The goal of most surgical treatments for stenosis is to decompress the nerve roots to relieve leg, groin, and/or buttock pain and other symptoms of neurogenic claudication secondary to lumbar spinal stenosis. A laminectomy procedure, with or without partial facetectomy, is a direct decompression, which removes the source of boney and ligamentous compression of the nerve roots. The treatment of spinal stenosis via laminectomy certainly has its place within a surgeon's armamentarium; however, for laminectomy to be a long term successful option, it has to be used for the proper patient. In addition, laminectomy procedures can be associated with significant adverse events related to the open surgical procedure, such as infection, as well as increased operative time and hospitalization following surgery when compared with interspinous spacer placement[18].

The laminectomy/direct decompression procedure is often able to effectively remove the neurologic compression. However, it is well-accepted that decompression alone in patients with spinal stenosis and degenerative spondylolisthesis predisposes patients to progression of instability if not stabilized at the time of decompression[19,20,21]. Consequently, lumbar spinal fusion following decompressive laminectomy is commonly recommended for this patient cohort to facilitate both neural decompression and motion segment stabilization. Here also, the increased complexity and invasiveness of the procedure offers greater potential for morbidity.

Recently, the coflex® Interlaminar Technology was PMA approved (P110008) for the treatment of spinal stenosis. It's important to recognize coflex® is intended for patients with a greater progression of stenosis than the X-STOP® patient population (moderate to severe stenosis). coflex® is designed to be utilized in conjunction with a decompression surgery to provide additional stabilization. To date, only data through 2 years has been published on this technology[22], although the data demonstrate the utility of coflex® as a treatment option for surgeons considering decompression and posterolateral fusion for their patients, in particular those patients who are at risk for spinal instability following decompression surgery.

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[18] Patil CG, Sarmiento JM, Ugiliweneza B, Mukherjee D, Nuno M, Liu JC, Walia S, Lad SP, Boakye M. Interspinous device versus laminectomy for lumbar spinal stenosis: a comparative effectiveness study. Spine J. 2014; 14:1484-92.

[19] Herkowitz HN, Kurz LT. Degenerative lumbar spondylolisthesis with spinal stenosis. A prospective study comparing decompression with decompression and intertransverse process arthrodesis. J Bone Joint Surg Am. 1991 Jul;73(6):802-8.

[20] Johnsson KE, Redlund-Johnell I, Uden A, Willner S. Preoperative and postoperative instability in lumbar spinal stenosis. Spine 1989; 14(6): 591-593.

[21] Mardjetko SM, Connolly PJ, Shott S. Degenerative lumbar spondylolisthesis: A meta-analysis of literature 1970-1993. Spine 1994; 19(20S):2256S-2265S.

[22] Davis RJ, Errico TJ, Bae H, Auerbach JD. Decompression and Coflex interlaminar stabilization compared with decompression and instrumented spinal fusion for spinal stenosis and low-grade degenerative spondylolisthesis: two-year results from the prospective, randomized, multicenter, Food and Drug Administration Investigational Device Exemption trial. Spine (Phila Pa 1976). 2013 Aug 15;38(18):1529-39.

Spinal fusion has well-documented shortcomings. Fusion surgery is more complex and invasive than a laminectomy in that the method for stabilization requires removal of the lamina bone and then implantation of pedicle screws and rods into the spine. Surgical dissection out to the tips of the transverse processes in order to achieve a posterolateral fusion requires extensive dissection and soft tissue trauma, which typically leads to more blood loss, longer operative times, significant scar tissue formation, and greater post-operative pain. Further, iliac crest bone graft harvest site pain following surgery is common and can be a persistent and debilitating source of continued pain in the post-operative period, despite having excellent relief from symptoms of spinal stenosis[23]. Long-term sequelae of the altered biomechanical environment may lead to progression of symptomatic disc degeneration at adjacent levels. The estimated rate of re-operation for symptomatic adjacent segment degeneration following lumbar spinal fusion is 36% at 10 years[24].

In conclusion, in the continuum of care from mild spinal stenosis to severe spinal stenosis, each treatment or device type is able to treat a certain patient sub-population. The Superion® device is intended to block extension and indirectly decompress the spine in a manner similar to the X-STOP® device. While the Superion® device is intended to treat the same patient population as the X-STOP® device, i.e., those with symptoms of neurogenic intermittent claudication secondary to moderate stenosis with intermittent neurogenic claudication, the minimally-invasive nature of the surgery and smaller overall device size are novel compared to other treatment options. This minimally-invasive procedure is designed to provide lower patient morbidity compared with open procedures like direct surgical decompression with or without additional stabilization, and further, does not alter or damage the spinal anatomy in any way, thereby preserving all potential future surgical options. In addition, in the event that device removal is appropriate, the Superion® implant may be removed using the same minimally-invasive technique – again without altering or damaging the spinal anatomy. As a result, the Superion® device is designed to provide a minimally-invasive option for treating patients with spinal stenosis, adding a novel treatment option for this patient population.

[23] Sasso RC, LeHuec JC, Shaffrey C; Iliac crest bone graft donor site pain after anterior lumbar interbody fusion: a prospective patient satisfaction outcome assessment. J Spinal Disord Tech. 2005 Feb;18 Suppl:S77-81.
[24] Ghiselli G, Wang JC, Bhatia NN, Hsu WK, Dawson EG Adjacent segment degeneration in the lumbar spine. J Bone Joint Surg Am. 2004 Jul;86-A(7):1497-503.

8. SUMMARY OF NON-CLINICAL DATA

A variety of mechanical and other non-clinical tests were conducted to characterize the performance of the Superion® device, including:

- Laboratory Studies
- Static Axial Compression
- Static Torsion
- Dynamic Axial Compression
- Dynamic Torsion
- Implant Deployment Under Load
- Static Torsion After Repeated Deployment Under Load
- Quantification and Characterization of Wear Debris
- Kinematic and Kinetic Behavior in Human Cadaver Spines
- Role of Supraspinous Ligament in Biomechanical Stability
- Effects of Implant on Canal and Foraminal Dimensions

Additional studies included:

- Sterilization Validation
- Shelf Life and Packaging Validation
- MRI Compatibility

Summaries of the testing, and of the results and findings of the testing, are provided in Appendix A.

9. SUMMARY OF CLINICAL DATA

The objective of the Superion® clinical trial was to evaluate the safety and effectiveness of the Superion® device compared to the X-STOP® control device for the treatment of symptoms of neurogenic intermittent claudication secondary to moderate lumbar spinal stenosis. The X-STOP® device was chosen as the control group for this study since the approved indications for use are similar to those sought for the Superion® device (moderate lumbar spinal stenosis with up to Grade 1 spondylolisthesis). In addition, direct decompression was not chosen as a control group, as direct decompression alone (without stabilization) is not considered the standard of care for treatment of lumbar spinal stenosis with the presence of Grade I spondylolisthesis.

A prospective, randomized, multi-center, concurrently controlled clinical study was conducted to compare the Superion® to the control, X-STOP®. A total of 470 patients were enrolled in the study, and 51 patients were post-consent screen failures prior to treatment. From the patients who met eligibility criteria, 28 non-randomized patients were assigned to the Superion® "training" cohort, while 391 patients were assigned to the modified Intent-to-Treat (mITT) cohort. Of these patients, 190 were randomized to Superion® and 201 to X-STOP®. The mITT served as the primary population for the final composite endpoint analysis for this PMA, which was approved in Supplement 016.

9.1. Inclusion/Exclusion Criteria

The inclusion and exclusion criteria for the study are presented in Table 5.

Table 5: Inclusion and Exclusion Criteria for the Superion® IDE

Inclusion Criteria: Enrollment in the Superion® study was limited to patients who met the following inclusion criteria:	**Exclusion Criteria:** Patients were not permitted to enroll in the Superion® study if they met any of the following exclusion criteria:
• Male or female subjects ≥ 45 years of age. • Persistent leg/buttock/groin pain, with or without back pain, that is relieved by flexion activities (example: sitting or bending over a shopping cart) • Subjects who have been symptomatic and undergoing conservative care treatment for at least 6 months. • Diagnosis of degenerative spinal stenosis of the lumbar spine, defined as the narrowing of the midline sagittal spinal canal (central) and/or narrowing between the facet superior articulating process (SAP), the posterior vertebral margin (lateral recess), and the nerve root canal (foraminal). • Radiographic confirmation of at least moderate spinal stenosis which narrows the central, lateral, or foraminal spinal canal at one or two	• Axial back pain only • Fixed motor deficit • Diagnosis of lumbar spinal stenosis which requires any direct neural decompression or surgical intervention other than those required to implant the control or investigational device • Unremitting pain in any spinal position • Significant peripheral neuropathy or acute denervation secondary to radiculopathy • Lumbar spinal stenosis at more than two levels determined pre-operatively to require surgical intervention • Significant instability of the lumbar spine as defined by ≥ 3mm translation or ≥ 5° angulation • Sustained pathologic fractures of the vertebrae or multiple fractures of the vertebrae and/or hips • Spondylolisthesis or degenerative spondylolisthesis

contiguous levels from L1-L5. Moderate spinal stenosis is defined as 25% to 50% reduction in lateral/central foramen compared to the adjacent levels, with radiographic confirmation of any one of the following: - Evidence of thecal sac and/or cauda equina compression - Evidence of nerve root impingement (displacement or compression) by either osseous or non-osseous elements - Evidence of hypertrophic facets with canal encroachment • Must present with moderately impaired Physical Function (PF) defined as a score of > 2.0 on the Zurich Claudication Questionnaire (ZCQ) • Must be able to sit for 50 minutes without pain and to walk 50 feet or more • Subjects who are able to give voluntary, written informed consent to participate in this clinical investigation and from whom consent has been obtained • Subjects, who, in the opinion of the Clinical Investigator, are able to understand this clinical investigation, cooperate with the investigational procedures and are willing to return for all the required post-treatment follow-ups.	greater than grade 1.0 (on a scale of 1-4) • Spondylolysis (pars fracture) • Degenerative lumbar scoliosis with a Cobb angle of > 10° at treatment level • Osteopenia or osteoporosis. To confirm eligibility, at the Clinical Investigator's discretion, the following subjects may have a DEXA scan performed: - Women 65 or older - Postmenopausal women < age 65 - Subjects with major risk factors for or diagnosed with osteoporosis or osteopenia If DEXA is required, exclusion is defined as a DEXA bone density measurement T score ≤ -2.5 • Morbid obesity, defined as Body Mass Index (BMI) greater than 40kg/m^2 • Insulin-dependent diabetes mellitus • Significant peripheral vascular disease (diminished dorsalis pedis or tibial pulses) • Prior surgery of the lumbar spine • Cauda equina syndrome (defined as neural compression causing neurogenic bowel or bladder dysfunction) • Infection in the disc or spine, past or present • Evidence of active (systemic or local) infection at time of surgery • Active systemic disease such as AIDS, HIV, hepatitis, etc. • Paget's disease at involved segment or metastasis to the vertebra, osteomalacia, or other metabolic bone disease • Currently undergoing immunosuppressive therapy or long-term steroid use • Known allergy to titanium or titanium alloys • Tumor in the spine or a malignant tumor except for basal cell carcinoma • Known or suspected history of alcohol and/or drug abuse • Prisoner or transient • Life expectancy less than two years • Angina, active rheumatoid arthritis, or any other systemic disease that would affect the subject's welfare or outcome of the clinical investigation • Any significant psychological disturbance past or present, psychotic or neurotic that could impair the consent process or ability to complete subject self-report questionnaires • Involved in pending litigation of the spine or worker's

	compensation related to the back • Enrolled in the treatment phase of another drug or device clinical investigation (currently or within past 30 days) • Congenital defect of the spine • Pregnant or lactating

The inclusion and exclusion criteria for the clinical study were developed to mimic the approved indication for the X-STOP® device, with the exception of including patients age 45-50, since the X-STOP® device is approved for age 50 and higher. Furthermore, the inclusion and exclusion criteria were designed to target the patient population having moderate stenosis, using criteria that would (a) include only patients having sufficiently advanced stenosis (i.e., those who no longer benefit from conservative care) to require surgical treatment for spinal stenosis, while (b) excluding those patients with severe spinal stenosis likely to require more extensive intervention.

While the exclusion criteria were designed to exclude patients needing direct neural decompression or surgical intervention other than those required to implant the control or investigational device, there were additional procedures performed. These procedures included a total of 9 Superion® patients (11 procedures) and 11 X-STOP® patients (16 procedures). These procedures included facet de-bulking (2 control), osteophyte removal (3 investigational, 3 control), and soft tissue removal (6 investigational, 13 control). All the procedures were performed to facilitate implant insertion and did not touch the lamina or provide any decompression, with the exception of a single X-STOP® subject with a laminectomy performed in conjunction with device implantation. This subject was excluded from the "Per Protocol" cohort due to this violation.

Patients had follow up examinations at discharge, 6 weeks, 3 months, 6 months, 12 months, 18 months, and 24 months, with annual follow-up visits thereafter.

The composite primary endpoint for the Superion® IDE was designed to measure safety, effectiveness, and risk-benefit profile of the Superion® device as compared to the X-STOP® device, and is composed of clinical outcome, safety, and radiographic parameters. The primary endpoint of the investigation was individual patient success, which required the patient to meet all of the following criteria at 24 month follow up:

- Clinically significant improvement in outcomes compared to baseline, as determined by meeting the criterion for at least two of three domains of ZCQ
  - $\geq$ 0.5 point improvement in physical function
  - $\geq$ 0.5 point improvement in symptom severity
  - Score of $\leq$ 2.5 points on patient satisfaction domain
- No re-operations, removals, revisions, or supplemental fixation at the index level(s)
- No major implant or procedure related complications
  - No dislodgement, migration, or deformation
  - New or persistent worsened neurological deficit at the index level
  - Spinous process fractures
  - Deep infection, death, or other permanent device attributed disability
- No clinically significant confounding treatments:

- No epidural injections or nerve block procedures at index level, spinal cord stimulators or rhizotomies

The statistical analysis plan specified a 10% non-inferiority margin to be utilized in the assessment of the primary endpoint, using a Bayesian analysis approach. The analysis plan pre-specified that missing data for the primary endpoint was to be handled using multiple imputation methodologies. Study success was defined *a priori* if the posterior probability of non-inferiority was at least 0.958, a value selected to control the type 1 error of the design (type 1 error < 0.05).

In addition, a number of secondary outcomes were measured, including clinically significant decreases in leg pain and back pain (measured by ≥20mm decrease in Visual Analog Scale [VAS]), maintenance or improvement of SF-12, and clinically significant decrease (defined as ≥15 point decrease vs. baseline) in Oswestry Disability Index (ODI), and to evaluate the maintenance of distraction. Radiographic assessments were also performed in the Superion® and X-STOP® groups by an independent radiographic core lab to determine qualitative radiographic measures (e.g., device migration or dislodgement, spinous process fracture) and quantitative radiographic measures (e.g., range of motion, disc angle, foraminal height).

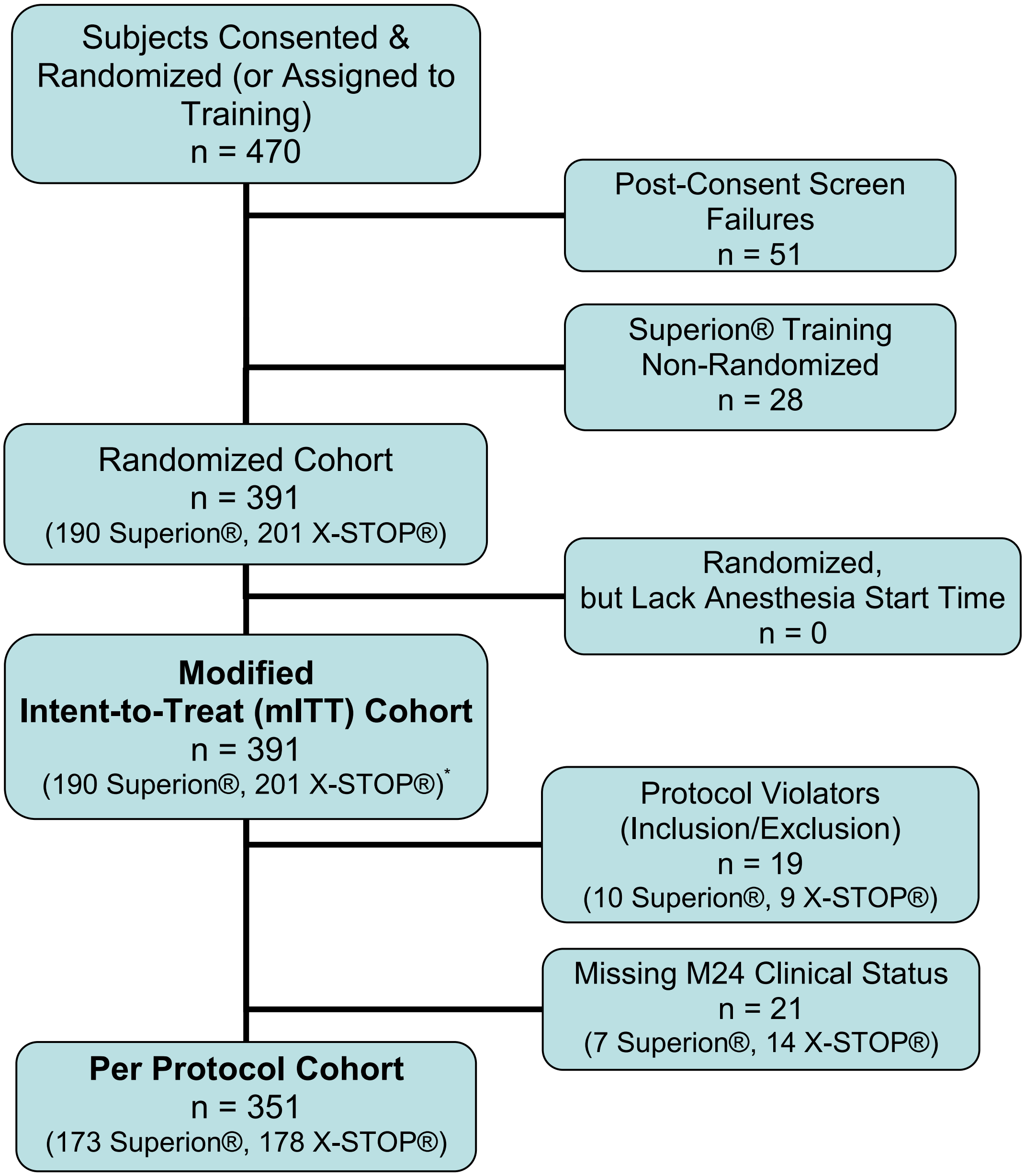
Adverse events were reported by the clinical study investigators. These events were reported by the investigator in each of the following categories:

- Event type
- Event severity (mild, moderate, severe)
- Whether the event was a serious adverse event (SAE) or not
- Relationship to the study device (yes, no, unknown/undetermined)
- Relationship to the study procedure (yes, no, unknown/undetermined)
- Relationship to the adjacent level (yes, no, unknown/undetermined)

An independent clinical events committee (CEC) composed of 3 clinicians not otherwise associated with the study reviewed adverse events deemed by the investigator to be device-related, procedure-related, adjacent level-related, or to have a relationship to the device, procedure, or adjacent level defined as "unknown/undetermined". To reduce reporting bias, the CEC had the ability to revise the classification of the adverse event, including changing the event type, event severity, presence or absence of SAE, and the relationship to the study device, procedure, or adjacent level. The safety results presented are those post-CEC review.

9.2. Patient Accounting

The patient accounting tree for the Superion® IDE is depicted in Figure 6.



*There were no subjects with misallocations of randomization, meaning all patients received the device to which they were randomized. As such, the mITT cohort is identical to the "As-Treated" patient cohort.

Figure 6: Patient Accounting Tree

Of the 51 post-consent screen failures, there were 2 patients in the training group and 49 that were randomized for the pivotal cohort that did not proceed to treatment. The 49 post-consent screen failures included 28 in the Superion® arm and 21 in the control arm. The patients that were post-consent screen failures were blinded to treatment group, and therefore, there was no bias introduced.

The primary analysis cohort for this study was the Modified Intent-to-Treat Cohort, defined as:

> "***Modified Intent-to-treat* patient population (mITT):** The mITT patient population will include all patients randomized and having an anesthesia start time, where patients will

be classified by the group in which they are randomized. Subjects with an anesthesia start time, but that do not receive a device, or receive the wrong device, will be failures."

Confirmatory analysis was performed in the Per Protocol Cohort, defined as:

"Per protocol (PP) Population: The PP patient population will include all subjects with 24-month follow-up data and no major protocol deviations and subjects that failed before 24 months."

Table 6: Patient Accounting Table for Superion® IDE

Date of data transfer 07/07/2014	Pre-Op		Week 6		Month 3		Month 6		Month 12		Month 18		Month 24		Month 36	
	I	C	I	C	I	C	I	C	I	C	I	C	I	C	I	C
(1) Theoretical follow-up	190	201	190	201	190	201	190	201	190	201	190	201	190	201	138	148
(2) Cumulative deaths	0	0	0	0	1	0	1	0	2	2	2	3	2	5	6	5
(3) Cumulative Revisions, Reoperations, and Injections	0	0	3	3	8	11	20	19	40	32	46	48	51	53	57	60
(4) Not Yet Overdue	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	4
(5) Deaths+term failures among theoretical due	0	0	3	3	9	11	21	19	42	34	48	51	53	57	42	54
(6) Expected due for clinic visit	190	201	187	198	181	190	169	182	148	167	142	150	137	144	95	90
(7) Failures among theoretical due	0	0	3	3	8	11	20	19	40	32	46	48	51	53	38	50
(8) Expected due+failures among theoretical due	190	201	190	201	189	201	189	201	188	199	188	198	188	197	133	140
All Evaluated Accounting (Actual [B]) Among Expected Due Procedures																
(9) # of procedures with any clinical data in interval	190	201	182	193	171	182	164	177	145	162	132	137	131	133	81	75
(10) All Evaluated Visit Compliance (%)	100%	100%	97.3%	97%	94.5%	95.8%	97.0%	97.3%	98.0%	97.0%	93.0%	91.3%	95.6%	92.4%	85.3%	83.3%
(11) ZCQ Responder status determined	190	201	181	193	171	182	164	177	145	162	132	137	131	133	81	75
(12) Radiographic evaluation	184	194	175	178	165	187	170	182	162	175	147	161	145	150	61	51
(13) Composite clinical success	190	201	184	196	179	193	184	197	185	195	179	187	183	187	120	128
(14) Actual[B] % Follow-up for CCS	100%	100%	96.8%	97.5%	94.5%	95.8%	97.0%	97.3%	98.0%	97.0%	93.0%	91.3%	97.3%	94.9%	90.2%	91.4%
Within Window Accounting (Actual [A]) Among Expected Due																
	I	C	I	C	I	C	I	C	I	C	I	C	I	C	I	C
(15) ZCQ Responder status determined	190	201	168	179	169	180	152	167	111	122	129	131	115	113	75	70
(16) Radiographic evaluation	184	194	162	162	162	186	154	169	123	131	138	152	127	128	56	48
(17) Composite clinical success	190	201	171	182	177	191	172	186	151	154	175	179	166	166	113	120
(18) Actual[A]% Follow-up for CCS	100%	100%	89.8%	90.4%	93.4%	94.7%	89.9%	91.8%	75.0%	73.1%	90.8%	87.3%	88.3%	84.3%	85.0%	85.7%

For the Superion® IDE, the Superion® cohort had a robust follow-up rate of 97.3% and the X-STOP® cohort had a follow-up rate of 94.9% through 24 months. For patients theoretically due for 36 month follow-up, the Superion® cohort had a follow-up rate of 90.2% and the X-STOP® cohort had a follow-up rate of 91.4%.

9.3. Patient Demographics

Baseline demographic information is presented in Table 7 and Table 8.

Table 7: Summary of Baseline and Demographic Continuous Variables - Superion® and X-STOP® mITT Analysis Set

	Superion®					X-STOP®					p[1]	Effect Size
Demographics	**N**	**Mean**	**SD**	**Min**	**Max**	**N**	**Mean**	**SD**	**Min**	**Max**		
Age at surgery (yrs)	190	66.9	9.4	47.0	88.0	201	66.2	10.2	46.0	89.0	0.291	0.06
Height (inches)	190	67.2	4.2	57.1	76.0	201	67.9	3.8	59.1	77.2	0.088	-0.19
Weight (lbs)	190	189.7	36.5	89.1	288.8	201	195.8	36.9	114.9	284.4	0.105	-0.17
BMI (k/m^2)	190	29.5	4.6	16.4	40.0	201	29.7	4.6	19.8	39.5	0.667	-0.05
Baseline Functional Status	**N**	**Mean**	**SD**	**Min**	**Max**	**N**	**Mean**	**SD**	**Min**	**Max**		
Oswestry (ODI)	190	39.1	13.4	8.9	74.0	201	39.9	11.6	6.7	80.0	0.477	-0.06
Zurich Claudication Qx Severity	190	3.33	0.64	1.6	5.0	201	3.37	0.61	2.0	5.0	0.489	-0.07
Zurich Claudication Qx Physical	190	2.63	0.43	1.6	3.6	201	2.72	0.43	1.8	3.8	0.033	-0.22
SF-12 PCS (Physical)	189	29.4	8.1	12.1	52.4	201	28.5	6.9	12.7	55.0	0.285	0.11
SF-12 MCS (Mental Health)	189	50.0	12.7	15.6	73.7	201	48.9	12.2	19.6	73.8	0.381	0.09
VAS Back pain	190	55.4	27.9	0.0	93.0	201	55.1	27.4	0.0	100.0	0.809	0.01
VAS Leg pain (right leg)	190	55.0	31.3	0.0	100.0	201	52.9	32.5	0.0	100.0	0.533	0.07
VAS Leg pain (left leg)	190	49.6	31.8	0.0	100.0	201	50.8	31.7	0.0	100.0	0.758	-0.04

Notes: [1] Wilcoxon rank sum tests for interval variables and ordinal variables.

Descriptive comparisons of device group mean differences at baseline and for device group differences over time and change from baseline over time were facilitated using Cohen's standardized effect size[25]. There were no differences in the baseline demographic parameters. The difference in Superion® baseline ZCQ Physical Function score and X-STOP® baseline ZCQ Physical Function was statistically significant (p=0.033), however, the difference is not clinically significant (> 0.5).

[25] Cohen, J. (1988). Statistical power analysis for the behavioral sciences (2nd ed.). New York: Academic Press.

Table 8: Summary of Baseline and Demographic Categorical Variables - Superion® and X-STOP® Control mITT Analysis Sets

	Superion®		X-STOP®		p[1]
	n	%	n	%	
Number of subjects	190		201		
Males	110	57.9	129	64.2	0.214
Females	80	42.1	72	35.8	
Race	n	%	n	%	
White	177	93.2	196	97.5	0.020
Asian	0	0.0	1	0.5	
African American	8	4.2	1	0.5	
American Indian or Alaska Native	0	0.0	0	0.0	
Native Hawaiian or Other Pacific Islander	0	0.0	1	0.5	
Other	5	2.6	2	1.0	
Ethnicity	n	%	n	%	
Hispanic or Latino	5	2.6	11	5.5	0.204
Not Hispanic or Latino	185	97.4	190	94.5	
Use of nicotine products	n	%	n	%	
No	89	46.8	101	50.2	0.809
Current Use	24	12.6	24	11.9	.
Previous Use	77	40.5	76	37.8	.

Note: [1] Fisher's exact test (2-sided).

Statistical analysis of baseline demographics shows no significant difference between patients randomized into the Superion® group compared to those randomized into the X-STOP® control group.

9.4. Perioperative Outcomes

Table 9: Perioperative Results from Superion® IDE (mean ± SD)

Operative Detail	Superion® (n=190)	X-STOP® (n=200)	p-value
Blood Loss (cc)	13.5 ± 15.9	38.7 ± 43.8	<0.001
Hospital Length of Stay (days)	1.80 ± 1.5	1.90 ± 1.5	0.046
Operative Time (min)	56.3 ± 26.8	47.2 ± 18.8	0.001

Some slight differences are apparent in perioperative metrics, including lesser estimated blood loss in the Superion® arm, and lesser operative time in the X-STOP® arm, which demonstrate a statistical difference, although the magnitude of these differences are not believed to be clinically meaningful.

9.5. Overall Treatment Success

9.5.1. Composite Clinical Success

The composite success measurement (i.e., the percentage of patients meeting primary endpoint criteria) was developed to measure the safety and effectiveness of the Superion® device when compared to the X-STOP® device for the treatment of lumbar spinal stenosis. This composite success measurement at 24 months includes measurements of clinical efficacy (Zurich Claudication Questionnaire [ZCQ] Success), safety (absence of revision or removal), absence of subsequent treatments (epidural steroid injection, rhizotomy, spinal cord stimulators), neurological success, and freedom from implant or procedure-related complications (absence of dislodgement, migration, spinous process fracture, or serious device-related adverse events).

Table 10: Superion® and X-STOP® Descriptive Comparisons of the Percentages of Patients Achieving the Primary Overall Success Efficacy Criterion[1] All Evaluated

	Number and Percentage Achieving Month 24 Overall Success						Posterior Probability of Non-Inferiority[1]
	Superion®			X-STOP®			
Analysis Cohort	N	n	%	N	n	%	
mITT	183	95	52.7%	187	93	50.2%	0.9927
Per Protocol	173	92	53.2%	178	88	49.4%	0.9944

[1]As described in the SAP for the mITT cohort, missing data for the posterior probability was handled using Bayesian multiple imputation methodologies. The %'s, as well as the posterior probability reported for the Bayesian multiple imputation (MI) are based on the mean over 5000 multiple imputations. The (SD's) over multiple imputations for these estimates were 52.7% (0.6%), 50.2% (0.9%), and 0.9927 (0.0045), respectively. The reported N and n values for this row reflect only the numbers of patients with complete Month 24 Composite Success. All 190 Superion® and 201 X-STOP® patients were included in the primary analysis of the mITT cohort using Bayesian multiple imputation, whereas all patients with missing primary endpoint data at 24 months were excluded from the Per Protocol cohort.

As demonstrated in Table 10, non-inferiority of the Superion® device was established in the primary effectiveness cohort due to a Bayesian Posterior Probability > 0.958 (as described in the statistical analysis plan), in the modified intent-to-treat (mITT) cohort that included all patients with an anesthesia start time in the Superion® IDE. Further, this demonstration of non-inferiority in the per protocol cohort provides confirmation of the non-inferiority result of the Superion® IDE and demonstrates the robustness of the overall statistical determination. Table 11 shows the success rates for each of the individual outcome measures that comprise the primary endpoint for the mITT cohort.

Table 11: Superion® and X-STOP® Control mITT Analysis Set - Descriptive Comparisons of the Percentages of Subjects Achieving Component Success at 24 Months

	Number and Percentage Meeting Criteria						
	Superion®			X-STOP®			
	N	n	%	N	n	%	p-value[1]
(1) ZCQ Responder (at least two of three ZCQ domains)	**131**	**107**	**81.7**	**133**	**116**	**87.2**	**0.237**
Improvement in physical function by ≥ 0.5 points	131	95	72.5	133	107	80.5	0.147
Improvement in symptom severity by ≥ 0.5 points	131	101	77.1	133	107	80.5	0.549
Mean satisfaction ≤ 2.5 points (1=very sat., 2=somewhat sat., 3=somewhat dis, 4=very dis.)	131	110	84.0	133	122	91.7	0.061
(2) No re-operations, revisions, removals or supplemental fixation at the index level(s)	**190**	**152**	**80.0**	**201**	**174**	**86.6**	**0.103**
(3) No major or implant procedure related complications defined as:	**190**	**164**	**86.3**	**201**	**166**	**82.6**	**0.332**
Failure from dislodgement or migration at any time	190	190	100.0	201	177	88.1	0.000
New or persistent worsened neurological deficit at the index level	150	143	95.3	157	152	96.8	0.566
Spinous process fractures at the index level(s)	190	169	88.9	201	191	95.0	0.038
Deep infection at the operative site requiring hospitalization, surgical draining, or IV antibiotics	190	190	100.0	201	199	99.0	0.499
Death or other permanent disability attributed to the device	190	190	100.0	201	201	100.0	.
(4) No clinically significant confounding treatments:	**190**	**165**	**86.8**	**201**	**167**	**83.1**	**0.325**
No epidural injections or nerve block procedures to treat spinal stenosis symptoms at the index level(s) at any time	190	165	86.8	201	168	83.6	0.395
No spinal cord stimulators or rhizotomies	190	190	100.0	201	200	99.5	1.000
Composite Clinical Success	**183**	**95**	**51.9**	**187**	**93**	**49.7**	**0.679**

Notes: [1] Fisher's Exact test; [2] Persistence was established by identifying new or worsening deficits at Month 18 that did not resolve by Month 24 including straight leg raise, muscle Strength, sensation to light touch, and sensation to pin prick.

The Superion® device provided a statistically similar proportion of patients yielding a clinically relevant improvement in ZCQ scores compared to the X-STOP® control. In terms of the reoperations and revisions sub-endpoint, the percentage of success in the X-STOP® control was only slightly higher than that of the Superion® group, though not a statistically significant difference. Conversely, the Superion® group had no failures from dislodgements or migrations, whereas the X-STOP® group had a lower success rate. The Superion® group also had a higher rate of success when the percentage of patients receiving epidural injections was considered, compared to the X-STOP® group. These results, while differing in some individual respects, in combination contributed to the Superion® and X-STOP® CCS success rates of 51.9% and 49.7%, respectively at the 24 month follow up timepoint.

With data available from a July 7, 2014, data lock, 3 year outcome data were calculated using the same parameters as the primary endpoint. The results from these 3 year outcome measurements are included in Table 12 and Table 13.

Table 12: Composite Success Results of Superion® IDE at 36 Months

	Number and Percentage Achieving Month 36 Overall Success					
	Superion®			X-STOP®		
Analysis Cohort	N	n	%	N	n	%
mITT	120	63	52.5%	129	49	38.0%

Table 13: Superion® and X-STOP® Control mITT Analysis Set - Descriptive Comparisons of the Percentages of Subjects Achieving Component Success at 36 Months

	Number and Percentage Meeting Criteria						
Date of data transfer 07/07/2014	Superion®			X-Stop®			
	N	n	%	N	n	%	p-value[1]
(1) ZCQ Responder (at least two of three ZCQ domains)	**81**	**71**	**87.7**	**75**	**63**	**84.0**	**0.646**
Improvement in physical function by ≥ 0.5 points	81	65	80.2	75	58	77.3	0.698
Improvement in symptom severity by ≥ 0.5 points	81	67	82.7	75	56	74.7	0.244
Mean satisfaction ≤ 2.5 points (1=very sat., 2=somewhat sat., 3=somewhat dis, 4=very dis.)	81	74	91.4	75	66	88.0	0.600
(2) No re-operations, revisions, removals or supplemental fixation at the index level(s)	**138**	**112**	**81.2**	**148**	**118**	**79.7**	**0.768**
(3) No major or implant procedure related complications defined as:	**138**	**125**	**90.6**	**148**	**126**	**85.1**	**0.206**
Failure from dislodgement or migration at any time	138	138	100.0	148	132	89.2	0.000
New or persistent worsened neurological deficit at the index level	113	109	96.5	112	108	96.4	1.000
Spinous process fractures at the index level(s)	138	125	90.6	148	141	95.3	0.164
Deep infection at the operative site requiring hospitalization, surgical draining, or IV antibiotics	138	138	100.0	148	146	98.6	0.499
Death or other permanent disability attributed to the device	138	138	100.0	148	148	100.0	.
(4) No clinically significant confounding treatments:	**138**	**120**	**87.0**	**148**	**118**	**79.7**	**0.115**
No epidural injections or nerve block procedures to treat spinal stenosis symptoms at the index level(s) at any time	138	120	87.0	148	119	80.4	0.152
No spinal cord stimulators or rhizotomies	138	138	100.0	148	147	99.3	1.000
Composite Clinical Success	**120**	**63**	**52.5**	**129**	**49**	**38.0**	**0.023**

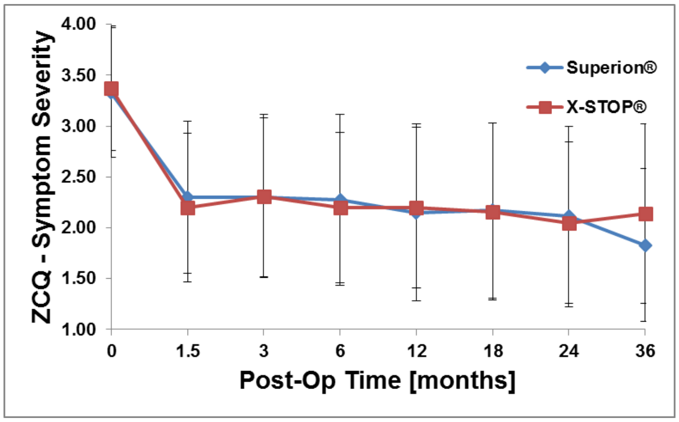
Notes: [1] Fisher's Exact test;

Significantly, the 36 month data demonstrates a maintenance in effectiveness for Superion® compared to the X-STOP® device, establishing durability of the treatment effect over the long term. Comparing the 24 month data with the 36 month data, there is a higher increase in X-STOP® re-operations, revisions, and removals (n=15) compared to the Superion® device (n=11), as well as a decrease in ZCQ scores. The incidence of spinous process fractures and migrations/dislodgements remained the same in both arms, establishing that no new observations of this type emerged at later time points. As demonstrated in Section 11, such radiographically-detected events generally occur within the first 6 months after surgery. It is unknown why the rate of reoperations, revisions, removals in the X-STOP® group increased between 24 and 36 months postoperatively. Given that there is convincing evidence that spinous process fractures remain fairly benign over the course of 24 months and into 36 months, the 36 month data further demonstrates the safety and effectiveness of Superion® device and also additional benefit compared to another indirect decompression option.

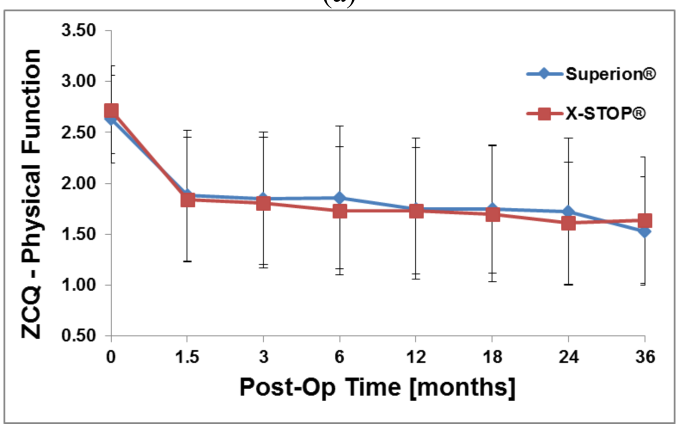
9.5.2. Individual Endpoints and Analyses

ZCQ

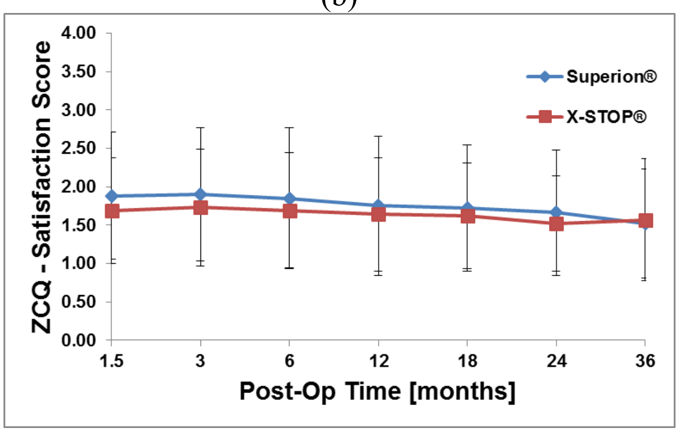
The time course of each of the sub-domains of the ZCQ is presented in Figure 7.



(a)



(b)



(c)

Figure 7: Time Course of Results (a) ZCQ Symptom Severity, (b) ZCQ Physical Function, (c) ZCQ Satisfaction

Overall, both cohorts exhibited similar decreases in Symptom Severity, Physical Function, and Satisfaction scores throughout the trial. At 24 months, the ZCQ mean scores for all three categories exhibited no statistically significant differences between the investigational and control cohorts although, as indicated above, there was some difference observed in favor of the Superion® device at the 3 year follow-up.

Reoperations, Revisions, and Supplemental Fixations

In the modified intent-to-treat patient population (mITT), there were a total of 49 reoperations or revisions in the Superion® group (49/190, 25.8%) compared with 44 reoperations or revisions in the X-STOP® group (44/201, 21.9%, p = 0.365) through the last available follow-up, which included time points past 24 months for many patients.

Through 24 months (as part of the primary endpoint), there were a total of 38 reoperations or revisions in the Superion® group (38/190, 20.0%) compared with 29 reoperations or revisions in the X-STOP® group (29/201, 14.4%, p = 0.179). Reoperations and revisions in patients prior to day 730 of treatment were considered to be failures in the primary endpoint although, as noted above, there was an increased number of reoperations and revisions in the X-STOP® arm, *vs*. the Superion® arm, at time points after 2 years.

Table 14: Reoperation and Revision Events in the Superion® Clinical Trial – Intent-to-Treat (mITT) Population

Reoperation or Revision Type	Treatment Group	Event Time Course (months)								Total (events)	Reasons
		<1.5	1.5-3	3-6	6-12	12-24	24-36	36-48	48-60		
Decompression and Device Removal	Superion®	-	3	4	8	4	7	-	-	26	20 leg and/or low back pain, 2 bone-related fracture, 2 neurological decline, 1 device deployment issue, 1 facet cyst
Device Removal and Fusion	Superion®	1	-	-	4	5	2	1	-	13	9 leg and/or low back pain, 2 bone-related fracture, 1 neurological decline, 1 unknown
Device Removal	Superion®	-	-	-	1	-	-	-	-	1	1 leg and/or low back pain
Fusion (no device removal)	Superion®	-	-	-	1	1	1	-	-	3	2 leg and/or low back pain, 1 synovial cyst
Supplemental Decompression	Superion®	-	-	2	1	1	-	-	-	4	3 leg and/or low back pain, 1 synovial cyst
I&D and Device Removal	Superion®	1	-	-	-	-	-	-	-	1	1 dural tear
Intraoperative Failure	Superion®	1							-	1	1 dural tear
Decompression and Device Removal	X-STOP®	1	1	3	3	8	4	2	1	23	18 leg and/or low back pain, 3 device dislodgement, 1 neurological decline, 1 herniated disc
Device Removal and Fusion	X-STOP®	-	-	-	1	5	5	2	-	13	12 leg and/or low back pain, 1 bone-related fracture
Device Removal	X-STOP®	-	-	-	1	-	1	-	-	2	1 leg and/or low back pain, 1 bone-related fracture
Device Replacement	X-STOP®	-	1	-	1	-	-	-	-	2	2 leg and/or low back pain
Intraoperative Failure	X-STOP®	2	-	-	-	-	-	-	-	2	2 bone-related fracture
Irrigation and Debridement	X-STOP®	2	-	-	-	-	-	-	-	2	2 deep infection

Similar rates of patients had decompression and device removal (13.7% Superion® vs. 11.4% X-STOP®, p = 0.543), device removal and fusion (6.8% Superion® vs. 6.5% X-STOP®, p = 1.000) and device removal (0.5% Superion® vs. 1.0% X-STOP®, p = 1.000), while a higher percentage of Superion® patients had supplemental decompression (2.1% vs. 0.0%, p = 0.055).

Two (2) X-STOP® patients had an intraoperative complication preventing implantation, compared with one (1) Superion® patient (1.0% vs. 0.5%, respectively, p = 1.000).

The primary reason for reoperation or revision in both Superion® and X-STOP® patients was related to progression of, or failure to adequately address, the symptoms of spinal stenosis. One could consider these "treatment failures," as would be expected to be observed with any therapy. The subsequent surgical procedures following device removal performed in the Superion® IDE were consistent with consensus clinical standards. In particular, for subjects without grade I spondylolisthesis, surgical decompression was performed. For patients with grade I spondylolisthesis, surgical decompression with fusion was performed.

Neurological Outcomes

Neurologic success was defined by the presence of no new or worsening neurologic deficit with respect to motor or sensory function. The rate of neurologic failures was similar for both Superion® and X-STOP® groups. The Superion® patient population had seven (7) patients (3.7%) that had new or worsening persistent motor or sensory neurologic assessments at 24 months, while the X-STOP® population had five (5) failures (2.5%) of these criteria.

Radiographic Failure Modalities

Based on the protocol, patients could be considered a composite success, or primary endpoint, failure for having particular radiographically-detected observations, such as spinous process fracture, device dislodgement, or device migration. This section of the Executive Summary details information associated with those patients meeting the pre-defined radiographic failure criteria. Of patients in the Superion® clinical study, there were 21 Superion® and 30 X-STOP® patients (11.1% vs. 14.9%, p=0.294) who had a radiographic failure as defined in the primary endpoint.

The rate of spinous process fractures at 24 months for both groups was 11.1% and 5.0% for Superion® and X-STOP® patients, respectively. The rate of migrations and dislodgements in the X-STOP® group was 11.9% and 0% in the Superion® group. In many cases, these fractures and device movements were asymptomatic and had no effect on the patient and their daily life through 24 months. It was noted, however, that in some cases of dislodgements and migrations, some clinical significance after the event occurred. As discussed in Section 11, those patients that had an X-STOP® migrate or dislodge showed an increase in VAS back pain scores (i.e., worsening pain) through 24 months and in many cases had higher pain and function (ZCQ) scores at 24 months compared to those patients in which their device did not migrate or dislodge. Notably, this same scenario was not seen in patients that had a spinous process fracture.

In conclusion, the rate of radiographic failure was comparable in both Superion® and X-STOP® cohorts. The rate of spinous process fractures was higher in the Superion® arm, but in both device cohorts there was little clinical significance associated with spinous process fractures. As further demonstrated in Section 11, the majority of spinous process fractures in both treatment groups were asymptomatic. X-STOP® patients did demonstrate a statistically and clinically significant difference in migrations and dislodgements, with no dislodgements or migrations occurring in the Superion® group, while 24 X-STOP® patients had their device migrate or dislodge.

Additional Treatments (Epidurals, Rhizotomies and Spinal Cord Stimulators)
Following index surgery, 25 of the 190 (13.2%) Superion® mITT subjects received an epidural steroid injection or nerve block at the level(s) of surgery prior to Month 24 and are considered study failures as a result. In contrast, 33 of the 201 (16.4%) X-STOP® mITT subjects received an epidural steroid injection or nerve block at the level(s) of surgery prior to Month 24 (p=0.395). Based on FDA discussions, prior precedent, and the use of epidurals as a supplemental treatment for patient pain at the treated level, all patients who received an epidural steroid injection or nerve block at the level(s) of surgery prior to Month 24 and were considered study failures.

Following index surgery, 0 of the 190 (0.0%) Superion® mITT subjects received a rhizotomy at the level(s) of surgery prior to Month 24. One (1) of the 201 (0.5%) X-STOP® mITT subjects received a rhizotomy and was therefore considered a study failure (p = 1.000). No subject in either group received a spinal cord stimulator at the level(s) of surgery prior to Month 24.

9.5.3. Secondary Endpoints and Analyses

Additional clinical and radiographic outcome measurements were utilized to determine the effect of the Superion® device compared to the X-STOP® device. Scores from the Oswestry Disability Index (ODI), Visual Analog Scale (VAS) Back, VAS Right Leg, VAS Left Leg, VAS Worst Leg, and the SF-12 were analyzed. Success proportions were also defined as ≥15 point ODI improvement, ≥20mm VAS improvement, and 0.5 point SF-12 improvement, all compared to baseline. Radiographic measurements were performed in both groups by an independent radiographic core lab to determine quantitative and qualitative measurements. Results of secondary endpoint analyses at 24 months are located in Table 15.

Table 15: Secondary Endpoints at 24 Month Follow-Up in Superion® Clinical Trial

Outcome Measure	Superion® n/N (%)	X-STOP® n/N (%)	p-value[1]
ODI: ≥15 point decrease	83/131 (63.4%)	89/133 (66.9%)	0.606
VAS Back: ≥20mm decrease	88/131 (67.2%)	91/133 (68.4%)	0.895
VAS Leg (Worse): ≥20mm decrease	99/131 (75.6%)	103/133 (77.4%)	0.772
SF-12 Physical Function: Maintenance or Improvement	103/128 (80.5%)	119/133 (89.5%)	0.055
SF-12 Mental Health: Maintenance or Improvement	77/128 (60.2%)	89/133 (66.9%)	0.303

[1]Fisher's Exact Test

Patients in the Superion® group exhibited a similar success proportion with all secondary endpoints when compared to the X-STOP® group.

The time-course of treatment effect is illustrated in Figure 8 for ODI and Figure 9 for back and leg pain (via VAS).

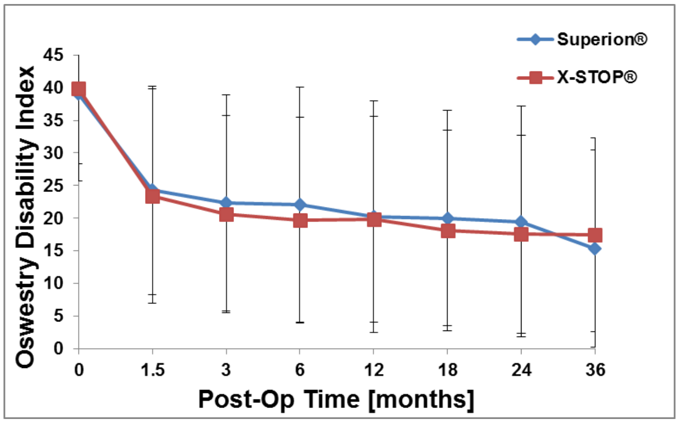
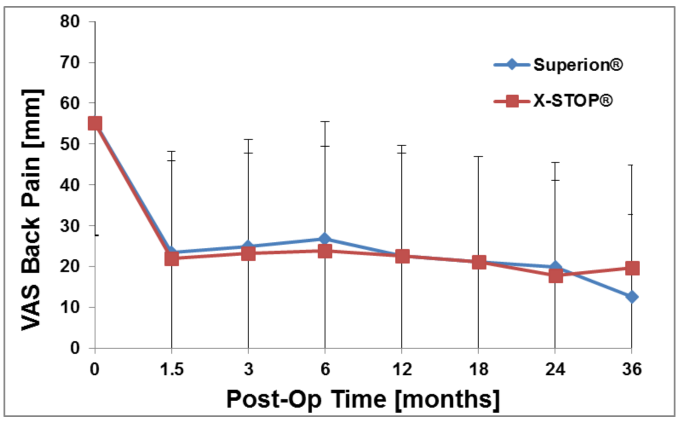
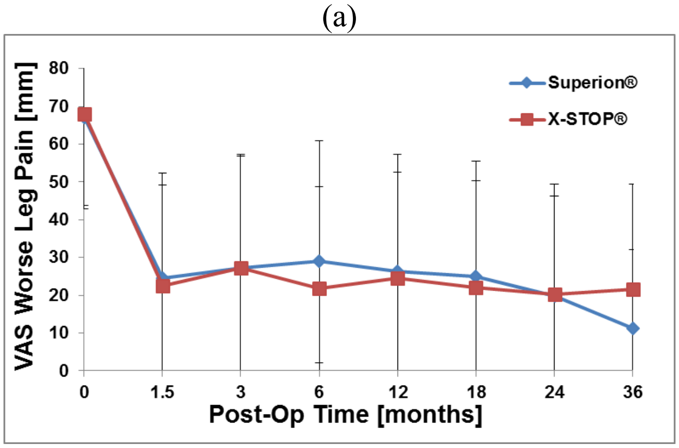


Figure 8: Time Course of Results for ODI



(a)



(b)

Figure 9: Time Course of Results (a) Back Pain via VAS, (b) Leg Pain (Worse) via VAS

The secondary endpoints related to stenosis and back function demonstrate a pronounced treatment effect, with decreases in mean ODI and mean back and leg pain (via VAS) from pre-operative values. This treatment effect is similar for both Superion® and X-STOP® patients, occurs primarily within the first 6 weeks of treatment, and is retained through 24 months. The Superion® results also demonstrated a maintenance of treatment effect at 36 months.

Radiographic Data

Quantitative range of motion data is presented in Table 16 and Table 17.

Table 16: Flexion Extension - Rotation (F to E) (deg), Superion® and X-STOP® ITT Analysis Sets

	Superion®						X-STOP®								
	At Level(s) of Implant (per level)												t-test	Wilcoxon	Effect
	N	Mean	SD	Med	Min	Max	N	Mean	SD	Med	Min	Max	p-value [1]	p-value [2]	Size [3]
Pre-Op	274	4.41	3.47	3.7	-9.3	17.0	288	4.60	3.39	3.6	0.0	18.6	0.522	0.518	-0.05
Month 24	176	3.21	2.72	2.3	0.0	11.8	176	4.01	3.23	3.0	0.0	16.8	0.012	0.017	-0.27

Notes:
[1] Two sample pooled t-test p-value
[2] Two sample Wilcoxon rank sum test p-value
[3] Standardized effect size (group difference in means divided by pooled within group SD).

Table 17: Translation (F to E) (mm), Superion® and X-STOP® ITT Analysis Sets

	Superion®						X-STOP®								
	At Level(s) of Implant (per level)												t-test	Wilcoxon	Effect
	N	Mean	SD	Med	Min	Max	N	Mean	SD	Med	Min	Max	p-value [1]	p-value [2]	Size [3]
Pre-Op	269	1.00	0.87	0.8	-1.4	4.1	288	1.05	0.90	0.9	-0.1	4.4	0.494	0.757	-0.06
Month 24	176	0.98	0.84	0.8	-0.7	4.9	174	1.09	0.88	1.0	0.0	4.4	0.221	0.232	-0.13

Notes:
[1] Two sample pooled t-test p-value
[2] Two sample Wilcoxon rank sum test p-value
[3] Standardized effect size (group difference in means divided by pooled within group SD).

Radiographic analysis of the Superion® and X-STOP® devices at 24 months post-op showed no disassembly or device collapse. Quantitative and qualitative radiographic data demonstrates both devices block extension, in particular the flexion-extension data. Quantitative measurements of foraminal height and disc angle demonstrate an increase in foraminal height immediately post-operatively for both treatments, with a slightly larger increase in foraminal height in the X-STOP® group.

The quantitative radiographic data demonstrates that both Superion® and X-STOP® devices provide distraction of the implanted spinal segment, generally resulting in an improvement in spinal stenosis symptoms. However, the distraction offered by the two devices is slightly different. In the X-STOP® group, there is a greater increase in spinous process distance and foraminal height when comparing the post-operative and 6 week changes from the pre-operative measures, although both devices achieve a substantial changes in quantitative radiographic outcomes following implantation. This X-STOP® device positioning creates a “levering effect”, whereby the posterior disc height increased, anterior disc height decreased, and the disc angle was reduced. Transitioning to the posterior spinal column, the foraminal height is increased for both groups by device placement.

The X-STOP® distraction and “wedging” that stems from its positioning causes a greater initial foraminal height increase. This phenomenon is also observed in the spinous process distance results, where the spinous process distance is increased more for X-STOP® patients than Superion®. These changes to the posterior column directly affected qualitative measures, however. The X-STOP® geometry interfaced with the irregularly shaped spinous processes and led to a “wedging” effect that resulted in significantly more migrations and expulsions as the device was forcibly re-positioned. In contrast, the Superion® performed more as a “block” to extension, with a smaller contact area, and no incidence of dislodgement.

9.5.4. Exploratory Analyses

Additional exploratory analyses were performed to demonstrate the poolability of several baseline patient cohorts and implantation procedures. Baseline patient cohorts included presence or absence of spondylolisthesis, smoking status, classification of stenosis, learning curve, supraspinous ligament repair, anesthesia type, and other covariates that may have influenced clinical outcomes.

Baseline differences in spondylolisthesis, smoking status, classification of stenosis, learning curve, supraspinous ligament repair, anesthesia type, and other covariates did not have an overall impact on the clinical success of patients receiving either Superion® or X-STOP®.

Table 18: Superion® IDE Composite Success Stratified by Demographic – Related Subgroups (mITT Population)

	Superion®	X-STOP®	p-value
Age			
<67 Years	50.0% (44/88)	54.5% (54/99)	0.560
≥67 Years	53.7% (51/95)	44.3% (39/88)	0.237
BMI			
<29.5	55.9% (57/102)	46.7% (42/90)	0.247
≥29.5	46.9% (38/81)	52.6% (51/97)	0.547
Presence of Orthopedic Comorbidities			
Yes	50.9% (59/116)	48.8% (63/129)	0.799
No	53.7% (36/67)	51.7% (30/58)	0.859
Nicotine Use			
Yes	46.9% (45/96)	52.2% (47/90)	0.557
No	57.5% (50/87)	47.4% (46/97)	0.186

Table 19: Superion® IDE Composite Success Stratified by Indication – Related Subgroups (mITT Population)

	Superion®	X-STOP®	p-value
Levels Treated			
1-level	55.2% (53/90)	48.4% (46/95)	0.386
2-level	48.3% (42/87)	51.1% (47/92)	0.766
Spondylolisthesis			

	Superion®	X-STOP®	p-value
Grade 1 Spondylolisthesis	57.4% (39/68)	56.0% (42/75)	0.691
No Spondylolisthesis	48.7% (56/115)	45.5% (51/112)	1.000
Stenosis Type			
Central Only	53.1% (34/64)	44.8% (26/58)	0.691
Lateral Only	31.3% (5/16)	46.7% (7/15)	0.473
Mixed	54.4% (56/103)	52.6% (60/114)	0.892
Surgical Approach (Superion® Only)			
Mini-Open	51.1% (46/90)	-	-
Percutaneous	52.8% (47/89)	-	-

Additional exploratory analyses related to radiographic observations are included in Section 11.

9.6. Adverse Events

The safety profile of the Superion® device is similar to the X-STOP® device when considering adverse event incidence. Table 20 summarizes adverse events in the clinical trial that occurred perioperatively or post-operatively, and those that were related to the device or procedure. No device-, or procedure-related deaths were reported during follow up in either the Superion® or X-STOP® control groups.

Table 20: Comparisons of Summary Adverse Event Rates between Superion® and X-STOP® mITT Analysis Sets

	Superion® (I) (N=190)		X-STOP® (C) (N=201)		I vs. C		
	n	%	n	%	Diff	LB	UB
Any adverse event (per patient)	180	94.7	184	91.5	-3.2	-13.1	6.8
Any device related AE	22	11.6	15	7.5	-4.1	-14.0	5.8
Any procedure related AE	27	14.2	32	15.9	1.7	-8.2	11.6
Any serious AE	88	46.3	92	45.8	-0.5	-10.5	9.4
Serious AE that is either device or procedure related	16	8.4	19	9.5	1.0	-8.9	10.9
Deaths	6	3.2	5	2.5	-0.7	-10.6	9.3

Notes:
[1] Exact 95% confidence interval for the group difference.

During the clinical study, adverse events were classified for device or procedure-relation as definitively “yes” or “no”, or having an “unknown/undetermined” relationship. At FDA request, an additional assessment was performed that grouped adverse events with an “unknown/undetermined” assessment for device and procedure relation with those events deemed to have a definite device or procedure relation as a "worst case" assessment. These results are presented in Table 21.

Table 21: Comparisons of Summary Adverse Event Rates between Superion® and X-STOP® mITT Analysis Sets

	Superion® (I) (N=190)		X-STOP® (C) (N=201)		I vs. C		
	n	%	n	%	Diff	LB	UB
Any adverse event (per patient)	180	94.7	184	91.5	-3.2	-13.1	6.8
Any device related AE[2]	73	38.4	79	39.3	0.9	-9.0	10.8
Any procedure related AE[2]	72	37.9	99	49.3	11.4	1.4	21.1
Any serious AE	88	46.3	92	45.8	-0.5	-10.5	9.4
Serious AE that is either device or procedure related	40	21.1	47	23.4	2.3	-7.6	12.2
Deaths	6	3.2	5	2.5	-0.7	-10.6	9.3

Notes:
[1] Exact 95% confidence interval for the group difference.
[2] Includes "Yes" and "Unknown/Undetermined" relationships

There were no trends or statistical differences within any of the device-related or surgery-related categories of adverse events, with the exception of "any procedure related AEs," which were statistically different when combining adverse events with definite and "unknown/undetermined" relation to the study procedure. The Superion® device demonstrated a reasonable assurance of safety when used to treat moderate stenosis. The event rates were minimal and very similar when comparing Superion® rates to X-STOP® rates. However, it is still important to understand some of the various events in more detail to better understand patient outcomes to improve labeling, training, or patient selection. It was determined that it is important to understand the patients that were noted as having pain events, wound-related events, and a return of spinal stenosis symptoms related to the device or procedure.

Specific adverse events are listed in Table 22, Table 23, and Table 24.

Table 22: Specific Adverse Events in Superion IDE (mITT cohort)

	Superion® (I) (N=190)			X-STOP® (C) (N=201)			I vs C		
Adverse Event Type	**No. of Events**	**No. of Pts.**	**% of Pts.**	**No. of Events**	**No. of Pts.**	**% of Pts.**	**Diff**	**LB**	**UB**
Abdominal pain	1	1	0.5	0	0	0.0	-0.5	-10.4	9.4
Allergic reaction	4	4	2.1	6	6	3.0	0.9	-9.0	10.8
Anemia	4	3	1.6	1	1	0.5	-1.1	-11.0	8.8
Angina	3	3	1.6	0	0	0.0	-1.6	-11.5	8.3
Back pain	56	50	26.3	71	66	32.8	6.5	-3.4	16.4
Bronchitis	2	2	1.1	6	5	2.5	1.4	-8.5	11.3
Cerebrovascular accident (CVA)	2	2	1.1	1	1	0.5	-0.6	-10.5	9.4
Chronic obstructive pulmonary disease (COPD)	0	0	0.0	0	0	0.0	.	.	.
Coronary episode, ischemic	3	2	1.1	5	2	1.0	-0.1	-10.0	9.9
Deep infection at the operative site	0	0	0.0	3	2	1.0	1.0	-8.9	10.9
Deep vein thrombosis	2	2	1.1	1	1	0.5	-0.6	-10.5	9.4
Device breakage preventing device placement	0	0	0.0	0	0	0.0	.	.	.
Device deformation preventing device	1	1	0.5	0	0	0.0	-0.5	-10.4	9.4
Diabetes mellitus	0	0	0.0	2	2	1.0	1.0	-8.9	10.9
Diabetes mellitus inadequate control	0	0	0.0	1	1	0.5	0.5	-9.4	10.4
Dizziness	5	5	2.6	0	0	0.0	-2.6	-12.5	7.3
Dural leaks	6	6	3.2	3	3	1.5	-1.7	-11.6	8.3
Dyspnea	0	0	0.0	1	1	0.5	0.5	-9.4	10.4
Edema	2	2	1.1	4	4	2.0	0.9	-9.0	10.8
Fever	0	0	0.0	4	4	2.0	2.0	-7.9	11.9
Gallstones	0	0	0.0	1	1	0.5	0.5	-9.4	10.4
Gastroesophageal reflux disease (GERD)	1	1	0.5	0	0	0.0	-0.5	-10.4	9.4
Gastrointestinal (GI) bleed	2	2	1.1	1	1	0.5	-0.6	-10.5	9.4
Headache	1	1	0.5	5	5	2.5	2.0	-7.9	11.9
Hematoma	0	0	0.0	1	1	0.5	0.5	-9.4	10.4
Infection	15	14	7.4	17	16	8.0	0.6	-9.3	10.5
Injury, Accidental	20	15	7.9	22	19	9.5	1.6	-8.4	11.4
Instruments breakage or malfunction preventing device placement	0	0	0.0	0	0	0.0	.	.	.
Leg pain	41	37	19.5	54	47	23.4	3.9	-6.0	13.8
Loss of bladder control	0	0	0.0	2	2	1.0	1.0	-8.9	10.9

Table 23: Specific Adverse Events in Superion IDE (mITT cohort, cont)

		Superion® (I) (N=190)			X-STOP® (C) (N=201)		I vs C		
Adverse Event Type	**No. of Events**	**No. of Pts.**	**% of Pts.**	**No. of Events**	**No. of Pts.**	**% of Pts.**	**Diff**	**LB**	**UB**
Loss of bowel control	0	0	0.0	0	0	0.0	.	.	.
Muscle damage	1	1	0.5	1	1	0.5	0.0	-9.9	9.9
Myocardial Infarction	5	5	2.6	3	3	1.5	-1.1	-11.0	8.8
Nausea	0	0	0.0	4	4	2.0	2.0	-7.9	11.9
Nerve root damage	0	0	0.0	0	0	0.0	.	.	.
Neurological disorder	27	22	11.6	13	13	6.5	-5.1	-15.0	4.8
Pain - buttock or groin	23	21	11.1	13	13	6.5	-4.6	-14.5	5.3
Pneumonia	5	4	2.1	5	5	2.5	0.4	-9.5	10.3
Presence of osteophyte formation associated with severe disc or facet degeneration	1	1	0.5	1	1	0.5	0.0	-9.9	9.9
Pulmonary edema	0	0	0.0	1	1	0.5	0.5	-9.4	10.4
Pulmonary embolism	1	1	0.5	0	0	0.0	-0.5	-10.4	9.4
Renal failure	3	3	1.6	1	1	0.5	-1.1	-11.0	8.8
Renal insufficiency	2	2	1.1	2	2	1.0	-0.1	-10.0	9.9
Respiratory disorder	4	3	1.6	4	4	2.0	0.4	-9.5	10.3
Respiratory distress	2	2	1.1	0	0	0.0	-1.1	-11.0	8.9
Respiratory infection	0	0	0.0	2	2	1.0	1.0	-8.9	10.9
Rheumatoid arthritis	1	1	0.5	0	0	0.0	-0.5	-10.4	9.4
Sensory loss	3	2	1.1	4	4	2.0	0.9	-9.0	10.8
Shortness of breath	0	0	0.0	1	1	0.5	0.5	-9.4	10.4
Soft tissue damage	1	1	0.5	7	7	3.5	3.0	-7.0	12.9
Spinal stenosis symptoms at index level	37	35	18.4	38	34	16.9	-1.5	-11.4	8.4
Spinous process fracture	24	22	11.6	14	13	6.5	-5.1	-15.0	4.8
Stroke	1	1	0.5	1	1	0.5	0.0	-9.9	9.9
Syncope	0	0	0.0	2	2	1.0	1.0	-8.9	10.9
Transient ischemic attack (TIA)	0	0	0.0	1	1	0.5	0.5	-9.4	10.4
Urinary tract infection	8	7	3.7	6	6	3.0	-0.7	-10.6	9.2
Vertebral compression fractures	1	1	0.5	3	3	1.5	1.0	-8.9	10.9
Wound dehiscence or delayed healing	0	0	0.0	1	1	0.5	0.5	-9.4	10.4
Wound drainage	1	1	0.5	4	4	2.0	1.5	-8.4	11.4
Other, specify	15	14	7.4	10	5	2.5	-4.9	-14.8	5.1

Table 24: Specific Adverse Events in Superion IDE (mITT cohort, cont)

	Superion® (I) (N=190)			X-STOP® (C) (N=201)			I vs C		
Adverse Event Type	**No. of Events**	**No. of Pts.**	**% of Pts.**	**No. of Events**	**No. of Pts.**	**% of Pts.**	**Diff**	**LB**	**UB**
Adjacent Level DDD	1	1	0.5	1	1	0.5	0.0	-9.9	9.9
Adjacent Level Stenosis	1	1	0.5	4	2	1.0	0.5	-9.4	10.4
Cancer/Neoplasm	13	11	5.8	14	13	6.5	0.7	-9.3	10.6
Cardiovascular	25	20	10.5	20	16	8.0	-2.6	-12.5	7.4
Device Dislodgement	1	1	0.5	2	2	1.0	0.5	-9.4	10.4
Device Migration	1	1	0.5	8	7	3.5	3.0	-7.0	12.9
Device Erosion	0	0	0.0	0	0	0.0	.	.	.
Device Subsidence	4	4	2.1	0	0	0.0	-2.1	-12.0	7.8
Dextroscoliosis	0	0	0.0	0	0	0.0	.	.	.
Disc Bulge	0	0	0.0	0	0	0.0	.	.	.
EENT	2	2	1.1	0	0	0.0	-1.1	-11.0	8.9
Endocrine/Metabolic	11	11	5.8	13	11	5.5	-0.3	-10.2	9.6
Facet Cyst	4	3	1.6	0	0	0.0	-1.6	-11.5	8.3
Genitourinary	25	22	11.6	17	17	8.5	-3.1	-13.0	6.8
Immune	0	0	0.0	1	1	0.5	0.5	-9.4	10.4
Dental	0	0	0.0	2	2	1.0	1.0	-8.9	10.9
Multi-Level DDD	1	1	0.5	0	0	0.0	-0.5	-10.4	9.4
Musculoskeletal	108	78	41.1	100	70	34.8	-6.2	-16.1	3.7
Ophthalmic	10	8	4.2	6	6	3.0	-1.2	-11.1	8.7
Pain-Back & Buttock	1	1	0.5	0	0	0.0	-0.5	-10.4	9.4
Pain- Back & Leg	0	0	0.0	0	0	0.0	.	.	.
Pain – Back & Hip	1	1	0.5	0	0	0.0	-0.5	-10.4	9.4
Pain- Buttock	1	1	0.5	2	2	1.0	0.5	-9.4	10.4
Pain- Buttocks and Hip	0	0	0.0	0	0	0.0	.	.	.
Pain- Hip	2	2	1.1	3	3	1.5	0.4	-9.5	10.4
Psychiatric/Substance Abuse	1	1	0.5	4	4	2.0	1.5	-8.4	11.4
Skin and Subcutaneous Tissue	2	2	1.1	10	8	4.0	2.9	-7.0	12.8
Spinal stenosis symptoms associated with non-index condition	0	0	0.0	0	0	0.0	.	.	.
Synovial Cyst	0	0	0.0	0	0	0.0	.	.	.
Device Breakage	0	0	0.0	1	1	0.5	0.5	-9.4	10.4

		Superion® (I) (N=190)			X-STOP® (C) (N=201)		I vs C		
Adverse Event Type	**No. of Events**	**No. of Pts.**	**% of Pts.**	**No. of Events**	**No. of Pts.**	**% of Pts.**	**Diff**	**LB**	**UB**
Gastrointestinal	9	7	3.7	10	9	4.5	0.8	-9.1	10.7
Hematologic	0	0	0.0	2	2	1.0	1.0	-8.9	10.9
Osteolysis	0	0	0.0	1	1	0.5	0.5	-9.4	10.4
Peripheral Vascular Disorder	0	0	0.0	3	3	1.5	1.5	-8.4	11.4
Progression of underlying disease	0	0	0.0	1	1	0.5	0.5	-9.4	10.4

Specific adverse events where the difference between Superion® and X-STOP® were more than 2% are indicated in Table 25.

Table 25: Specific Adverse Events in Superion® IDE

	Superior® (I) (N=190)			X-STOP® (C) (N=201)			I vs C
Adverse Event Type	**No. of Events**	**No. of Pts.**	**% of Pts.**	**No. of Events**	**No. of Pts.**	**% of Pts.**	**p-value**
Back pain	56	50	26.3	71	66	32.8	0.184
Cardiovascular	25	20	10.5	20	16	8.0	0.389
Device Migration	1	1	0.5	8	7	3.5	0.068
Device Subsidence	4	4	2.1	0	0	0.0	0.055
Dizziness	5	5	2.6	0	0	0.0	0.026
Genitourinary	25	22	11.6	17	17	8.5	0.317
Leg pain	41	37	19.5	54	47	23.4	0.389
Musculoskeletal	108	78	41.1	100	70	34.8	0.212
Neurological disorder	27	22	11.6	13	13	6.5	0.110
Other, specify	15	14	7.4	10	5	2.5	0.033
Pain - buttock or groin	23	21	11.1	13	13	6.5	0.150
Skin and Subcutaneous Tissue	2	2	1.1	10	8	4.0	0.106
Soft tissue damage	1	1	0.5	7	7	3.5	0.068
Spinous process fracture	24	22	11.6	14	13	6.5	0.110

Pain-related adverse events were distributed differently between the Superion® and X-STOP® groups. X-STOP® patients were more likely to have back pain or leg pain adverse events, while Superion® patients were more likely to have buttock or groin adverse events. In addition, X-STOP® patients were more likely to have events related to device migration, skin and subcutaneous tissue, and soft tissue damage. In contrast, Superion® patients were more likely to have an adverse event related to spinous process fracture and neurological disorder. Spinous process fractures reported by the sites were heterogeneous in nature and included fracture types (such as posterior avulsions) that were not part of the grading criteria used in independent radiographic review. In addition, device migrations noted by the sites were also heterogeneous in nature without the use of specific grading criteria included in the independent radiographic review.

Overall, the adverse event rates between the Superion® and X-STOP® patients were similar, despite minor differences in the types of adverse events. While the different devices each had different associated adverse event rates associated with individual types of events, the balance of these events, either severe or non-severe, did not tip toward one device or another. Specifically, Superion® patients had more device-related adverse events, compared with X-STOP® patients. The procedure-related adverse events were statistically similar between the two groups, although numerically higher in the X-STOP® group. The data presented demonstrates a reasonable assurance of the safety of the Superion® device compared to an approved device (X-STOP®) for the same intended patient population of moderate stenosis with a positive benefit-risk profile.

9.7. Safety and Effectiveness Conclusion

The objective of the Superion® IDE was to demonstrate a reasonable assurance of safety and effectiveness through valid scientific evidence collected by means of a scientific study design, rigorous study conduct, and high level of patient accountability. A complex and clinical robust composite endpoint was developed in conjunction with the FDA to measure the safety and effectiveness of the Superion® device. When the data from the mITT population are analyzed per the approved protocol, the Superion® device demonstrates clinical non-inferiority compared to the control device on the basis of month 24 composite success in addition to a favorable risk-benefit profile. The posterior probability that Month 24 composite success achievement probability among Superion® procedures is no more than 0.10 less than the same value among X-STOP® procedures is equal to 0.9927, using the *a priori* defined primary endpoint. Further, available longer term clinical outcome data acquired through 36 months present additional data to support the safety and effectiveness profile of the Superion® device compared to the X-STOP® device. In addition, there were no observations or events that were not predicted (e.g., unanticipated adverse events) that would cause a different analysis of safety and effectiveness. Overall, the patients in both treatment groups demonstrated an immediate improvement in their stenosis symptoms and these were maintained through 24 months as measured by ZCQ. In addition, there were similar safety profiles of both treatment groups. Therefore, it is has been demonstrated Superion® is safe and effective with an established risk-benefit profile supporting use in the indicated patient population.

10. COMPARISON OF STUDY RESULTS TO PREVIOUS STUDIES

For patients with moderate stenosis, a number of treatments are available, depending on the other concomitant pathologies present in the patient's spine. Each of these treatments has a different risk-benefit profile, and these risk-benefit profiles along with the concomitant spinal pathologies must be taken into consideration when comparing different treatments for moderate stenosis.

10.1. X-STOP® IDE

The pivotal clinical study for the X-STOP® device was the basis for the determination of safety and effectiveness for that device. A comparison of the results of the original X-STOP® IDE and the Superion® IDE is provided below to demonstrate that the patient population for the Superion® IDE is consistent with the approved patient population for X-STOP®.

Patient enrollment parameters (i.e., inclusion/exclusion criteria) were nearly identical between the two studies that were both intended to treat a moderate stenosis population. A summary of the primary similarities is presented in Table 26.

Table 26: Comparison between Superion® and X-STOP® Studies

Parameter	X-STOP® (X-STOP® IDE)	X-STOP® (Superion® IDE)
Treatment	Conservative Treatment for at least 6 months	Conservative Treatment for at least 6 months
Pain	Persistent leg/buttock/groin pain, with or without back pain, that is relieved by flexion	Persistent leg/buttock/groin pain, with or without back pain, that is relieved by flexion
Age	≥ 50 years old	≥ 45 years old
Radiographic	Narrowing of spinal canal, nerve root canal, or intervertebral foramen (< 50% reduction)	Narrowing of central, lateral, or foraminal spinal canal (25% to 50% reduction in lateral/central foramen)
ZCQ	>2.0 ZCQ Physical Function	≥2.0 ZCQ Physical Function
Function	Must be able to sit for 50 minutes without pain and to walk 50 feet or more	Must be able to sit for 50 minutes without pain and to walk 50 feet or more
Pain Relief	Pain must be relieved in flexion	Pain must be relieved in flexion
Back Pain	Patients can have back pain with leg pain. Patients with back pain only are excluded.	Patients can have back pain with leg pain. Patients with back pain only are excluded.

The patient demographics for the X-STOP® population enrolled in the X-STOP® IDE and Superion® IDE population are presented in Table 27.

Table 27: Demographic Comparison

	X-STOP® (X-STOP® IDE)		X-STOP® (Superion® IDE)	
Demographics	**N**	**Mean**	**N**	**Mean**
Age at surgery (yrs)	100	70.0	201	66.2
Height (inches)	100	67.3	201	67.9
Weight (lbs)	100	177.1	201	195.8
Gender (Male)	57 (57.0%)		129 (64.2%)	
Gender (Female)	43 (43.0%)		72 (35.8%)	
Baseline Functional Status	**N**	**Mean**	**N**	**Mean**
Zurich Claudication Qx Severity	100	3.14	201	3.37
Zurich Claudication Qx Physical	100	2.48	201	2.72
SF-12 PCS (Physical)	100	27.8	201	28.5
SF-12 MCS (Mental Health)	100	51.5	201	48.9

The Superion® IDE enrolled patients who were slightly younger with higher body weight. Additionally, the baseline ZCQ scores were slightly higher in the Superion® IDE. These differences are not statistically significant; however, the slightly higher ZCQ scores in the Superion® IDE are indicative of a more moderate stenosis patient population having more severe or advanced symptoms, i.e., were "sicker" compared with those in the X-STOP® IDE. In total, the Superion® IDE was designed to include patients in the indicated population for the X-STOP® device rather than the exact population studied in the X-STOP® trial.

In the X-STOP® IDE, the composite endpoint included the following components:

- Clinically significant improvement in outcomes compared to baseline, as determined by meeting the criterion for **all three** domains of ZCQ
  - ≥ 0.5 point improvement in physical function
  - ≥ 0.5 point improvement in symptom severity
  - Score of ≤ 2.5 points on patient satisfaction domain
- No additional surgery for lumbar stenosis
- Maintained distraction
- No dislodgement
- Absence of implant-related complications

In the overall treated population, 44% of the X-STOP® patients achieved success in the primary endpoint, while 54% achieved success in a patient population with moderate stenosis, as defined in the population studied in the Superion® IDE.

A comparison of the ZCQ and reoperation outcomes between the Superion® IDE and X-STOP® IDE is included in Table 28.

Table 28: Comparison of Superion® IDE and X-STOP® IDE Results

Study/Group	ZCQ Success (All 3 Components)	Reoperation Rate
Superion® IDE, Superion®	88/144 (61.1%)	38/190 (20.0%)
Superion® IDE, X-STOP®	100/156 (64.1%)	27/201 (14.5%)
X-STOP® IDE, X-STOP® (all)	45/96 (47%)	10/96 (10.4%)
X-STOP® IDE, X-STOP® (indicated population)[1]	41/73 (56%)	7/73 (9.6%)
X-STOP® IDE, X-STOP® (indicated population, excluding Inventor Study Site)	22/52 (42%)	6/54 (11.1%)

[1]Sub-analysis in the X-STOP® IDE of patients who ultimately met the indicated population of moderate stenosis.

The clinical outcomes reported in the Superion® IDE (in both the X-STOP® and Superion groups) demonstrate higher ZCQ success rates than those presented in the X-STOP® IDE, particularly when considering results excluding the study site of the X-STOP® inventor. These results are expected, as greater experience with the X-STOP® device may have led to the improved clinical outcomes with its use.

It is important to note that the radiographic outcomes for the X-STOP® IDE are not readily comparable to those in the Superion® IDE, as the X-STOP® IDE only collected sporadic radiographic measurements, while the Superion® IDE collected radiographs at all follow up time periods for analysis by an independent core laboratory. As noted by several panel members during the August 2004 X-STOP® Advisory Panel meeting, the X-STOP® IDE study grossly lacked radiographic measurements. Panel member Dr. Kim noted "…x-rays in this study looks for only device failures and hardware complications". Therefore, asymptomatic radiographic observations were not reported and the resulting rates would be expected to be notably lower. Specifically, the incidence of spinous process fracture, migration, and dislodgement were reported in the X-STOP® IDE only when associated with an adverse event, indicating only patients with symptomatic radiographic observations would be reported. As stated above, the majority of the radiographic observations in the Superion® trial were asymptomatic. Since the majority of X-STOP® migration and dislodgements reported in the Superion® IDE trial did not require revision (21/24), similar rates of symptomatic device migration and dislodgement were observed in the two trials (1.5% for the Superion® trial and 1.0% for the X-STOP® PMA, p=1.000).

Overall, the results from the Superion® IDE demonstrate that the Superion® and X-STOP® devices achieved similar clinical success when compared to the results from the X-STOP® IDE.

10.2. Direct Decompression

Direct decompression of the spine is utilized in many surgical procedures to treat moderate to severe lumbar spinal stenosis. A direct decompression surgery removes the osseous and soft tissue creating impingement on the spinal nerve roots and column, thereby relieving a patient's spinal stenosis symptoms. Additional posterior stabilization in the form of posterolateral fusion with hardware (e.g., pedicle screw systems) or the coflex® Interlaminar Technology is often utilized in conjunction with a direct decompression, as the removal of bony tissue to relieve the patient's symptoms can create some mechanical instability in the affected motion segment.

Perioperative Outcomes and Adverse Events

The major benefit of indirect decompression compared to surgical decompression with or without stabilization is the minimally-invasive nature of the procedure that lends itself to shorter surgeries and lower rates of perioperative adverse events, such as infection. These benefits can be quantified by comparing perioperative outcomes between studies of indirect decompression and decompression with or without posterior stabilization.

The coflex® IDE utilized direct decompression for both treatment arms, followed by stabilization with coflex® or posterolateral fusion. A comparison of the Superion® IDE results to the results from the coflex® IDE (for moderate to severe spinal stenosis with back pain) highlights the differences in perioperative outcomes (Table 29). Even though these devices are indicated for different patient populations, the blood loss and operative time data provides incremental benefit to the risk-benefit profile for indirect decompression.

Table 29: Perioperative Results from Superion® IDE and coflex® IDE (mean ± SD)

Operative Detail	Superion® IDE		coflex® IDE	
	Superion®	X-STOP®	Decompression + coflex®	Decompression + Fusion
	(n=190)	(n=200)	(n=215)	(n=107)
Blood Loss (cc)	13.5 ± 15.9	38.7 ± 43.8	109.7 ± 120.0	348.6 ± 281.8
Hospital Length of Stay (days)	1.80 ± 1.5	1.90 ± 1.5	1.90 ± 1.08	3.19 ± 1.61
Operative Time (min)	56.3 ± 26.8	47.2 ± 18.8	98.0 ± 41.1	153.2 ± 55.5

As shown in the perioperative results from both Superion® and coflex® IDE studies, indirect decompression surgeries with both Superion® and X-STOP® demonstrated significantly less blood loss and operative time than surgical decompression with stabilization with coflex® or fusion. While the severity of stenosis and baseline patient demographics in these two studies are different, these results demonstrate the differences in operative time and patient morbidity (based on estimated blood loss) between indirect decompression and decompression with stabilization using coflex® or posterolateral fusion. These results are important to surgeons and patients who must weigh the risk-benefit profiles of indirect versus direct decompression when deciding a treatment course.

In addition, the coflex® IDE cited wound problems in 14.0% of all decompression + coflex® patients (with irrigation and debridement required for 1.9% of decompression + coflex® patients), while the Superion® IDE cited infection in only 2.6% of Superion® patients (with irrigation and debridement required for 0.5% of Superion® patients and 1.0% of X-STOP® patients).

Other studies in the literature demonstrate higher complication rates associated with direct decompression procedures compared to those demonstrated with interspinous spacers. A recently published retrospective study[26] comparing X-STOP® to a demographic-matched control of surgical decompression saw higher rates of complications within 30 days of index surgery for surgical decompression (9.2%) compared with X-STOP® (3.4%), as well as an increase in mean index hospitalization for surgical decompression (2.49 days) compared with X-STOP® (1.58 days).

Perioperative complication rates reported in the literature for direct decompression range from 10% to 29.6%[27,28,29], with greater complications associated when a fusion procedure is utilized for adjunctive stabilization[30]. These perioperative complications include infection, dural tear, hematoma, seroma, inflammatory reaction, pulmonary edema, urinary retention, and mechanical complications.

A recent review of spinal devices in the Medicare population reported higher complication rates in decompression surgeries compared to interspinous spacers[31]. Results of this assessment are presented in Table 30.

Table 30: Complication Rates Associated with Lumbar Spinal Stenosis Surgery, from Deyo et al. (2013)

	Interspinous Process Spacer	Interspinous Process Spacer + Decompression	Decompression Alone	Fusion
N for measures that include mortality	3,965	1,644	76,520	16,955
N for safety & utilization measures	3,912	1,617	75,310	16,623
Wound complications @ 30 days	30 (0.8%)	21 (1.3%)	1,343 (1.8%)	548 (3.3%)
Cardiopulmonary or stroke complications @ 30 days	39 (1.0%)	21 (1.3%)	1,192 (1.6%)	473 (2.9%)
Death w/in 30 days	7 (0.18%)	7 (0.43%)	240 (0.31%)	102 (0.60%)
Life-threatening complications (either of prior two rows)	45 (1.2%)	25 (1.6%)	1,351 (1.8%)	553 (3.3%)
All-cause rehospitalization within 30 days	175 (4.5%)	92 (5.7%)	4,985 (6.6%)	1,568 (9.4%)

These results demonstrate higher rates of perioperative complications associated with surgical decompression, with or without stabilization, compared with indirect decompression procedures,

[26] Patil CG, Sarmiento JM, Ugiliweneza B, Mukherjee D, Nuno M, Liu JC, Walia S, Lad SP, Boakye M. Interspinous device versus laminectomy for lumbar spinal stenosis: a comparative effectiveness study. Spine J. 2014; 14:1484-92.

[27] Fokter SK, and Yerby SA: Patient –based outcomes for the operative treatment of degenerative lumbar spinal stenosis. Eur Spine J, 2006. 15:1661-1669.

[28] Ciol MA, et al.: An Assessment of Surgery for Spinal Stenosis: Time Trends, Geographic Variations, Complications, and Reoprations. J Am Geriatric Soc, 1996. 44(3): 1-10.

[29] Atlas SJ, et al.: The Maine Lumbar Spine Study, Part III: 1-Year Outcomes of Surgical and Nonsurgical Management of Lumbar Spinal Stenosis. Spine, 1996. 21(15)1: 1787-1794.

[30] Deyo RA, et al.: Morbidity and mortality in association with procedures on the lumbar spine. The influence of age, diagnosis, and procedure. J Bone Joint Surg Am, 1992. 74-A(4): 536-543.

[31] Deyo RA, et al.: Interspinous Spacers Compared With Decompression or Fusion for Lumbar Stenosis. Complications and Repeat Operations in the Medicare Population. Spine, 2013. 38(10): 865-872.

such as Superion® and X-STOP®. While direct comparison of these results with the Superion® IDE are difficult due to differences in reporting, these results nonetheless align with the lower levels of wound-related complications demonstrated in the Superion® IDE compared with the results from the coflex® IDE (which utilized decompression plus coflex® or posterolateral fusion).

Clinical Outcomes

While there have been no large scale randomized clinical studies comparing interspinous devices to direct decompression for the treatment of moderate stenosis, clinical outcome measurements presented in published clinical studies can be compared to the results from the Superion® IDE to compare the effectiveness of these devices compared to direct decompression. While these studies did not utilize a robust composite endpoint (as was utilized in the Superion® IDE), comparison of individual clinical outcomes is possible. Studies of direct decompression using the same ZCQ success criteria as the Superion® IDE are presented in Table 31.

Table 31: Comparison of ZCQ Results of Decompression Studies to Superion® IDE

Article	n	Treatment	Time point	ZCQ Success (2 of 3)
Superion® IDE, Superion®	131	Superion®	24 months	81.7%
Superion® IDE, X-STOP®	133	X-STOP®	24 months	87.2%
Superion® IDE, Superion® (non-censored for injections)[1]	144	Superion®	24 months	80.6%
Superion® IDE, X-STOP® (non-censored for injections)[1]	156	X-STOP®	24 months	84.0%
Fokter et al., 2006[32]	58	Decompression	27 months (mean)	63.8%
Moojen et al., 2013[33]	79	Decompression	12 months	69%

[1]Subjects with epidural steroid or nerve root blocks are excluded from the assessments of clinical outcome measurements due to the masking effects these additional procedures may have on the clinical outcome measurements. For direct comparison to results from the literature, subjects with injections are included in this assessment.

In comparison to these ZCQ results, both treatment arms in the Superion® IDE achieved a higher rate of ZCQ success compared with patients undergoing decompression alone. In addition, leg pain improvement following laminectomy without posterior stabilization has been reported in 27-67% of subjects at 2 years[34,35,36], while 75.6% of Superion® subjects reported clinically significant leg pain improvement (via >20mm VAS decrease) at 2 years. These data indicate that Superion® performs similarly or better than direct decompression at 2 years postoperatively.

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[32] Fokter SK, Yerby SA. Patient-based outcomes for the operative treatment of degenerative lumbar spinal stenosis. Eur Spine J. 2006 Nov;15(11):1661-9.

[33] Moojen WA1, Arts MP, Jacobs WC, et al. Interspinous process device versus standard conventional surgical decompression for lumbar spinal stenosis: randomized controlled trial. BMJ. 2013 Nov 14;347:f6415.

[34] Haro H, Maekawa S, Hamada Y. Prospective analysis of clinical evaluation and self-assessment by patients after decompression surgery for degenerative lumbar canal stenosis. Spine J. Mar-Apr 2008;8(2):380-384.

[35] Malmivaara A, Slatis P, Heliovaara M, et al. Surgical or nonoperative treatment for lumbar spinal stenosis? A randomized controlled trial. Spine (Phila Pa 1976). Jan 1 2007;32(1):1-8.

[36] Stromqvist BH, Berg S, Gerdhem P, et al. X-Stop Versus Decompressive Surgery for Lumbar Neurogenic Intermittent Claudication: Randomized Controlled Trial With 2-Year Follow-up. Spine (Phila Pa 1976). Aug 1 2013;38(17):1436-1442.

10.3. Summary

Comparison of the results from the Superion® IDE to other studies in the literature demonstrate that the Superion® device provides similar rates of clinical success as other treatment options with a minimally-invasive surgical procedure and fewer perioperative complications.

11. RADIOGRAPHIC OBSERVATIONS IN THE SUPERION® IDE

As part of the Superion® IDE, independent review of all radiographic images was performed by a core laboratory, Medical Metrics, Inc. The independent review derived both qualitative and quantitative measurements performed by experts in radiographic review. In particular, all radiographs were reviewed for spinous process fracture, device migration, and device dislodgement by radiologists specifically trained in review of interspinous devices using strict, *a priori* defined criteria for each of these qualitative measurements. In contrast to the original clinical trial supporting PMA approval for the X-STOP® device, this review was meant to provide a high quality and standardized methodology to be utilized in the primary endpoint determination for the Superion® IDE.

The overall incidence of these radiographic observations is presented in Table 32.

Table 32: Subjects with Radiographic Observations in the Superion® IDE

Radiographic Observation	Superion® (n=190)		X-STOP® (n=201)	
	n	%	n	%
Spinous Process Fracture (any time)	31	16.3%	17	8.5%
Spinous Process Fracture (non-healed at 24 months)	21	11.1%	10	5.0%
Device Migration (>5mm)	0	0.0%	16	8.0%
Device Dislodgement	0	0.0%	20	10.0%
Any Radiographic Observation (any time)	31	16.3%	34*	16.9%
Any Radiographic Observation (24 months)	21	11.1%	28	13.9%

*Significant overlap was present in X-STOP® subjects having spinous process fractures, device migration, and device dislodgement.

Of note, these radiographic observations generally did not result in clinical outcome measurements that differ from the overall population. In particular, patients having spinous process fractures did not have a higher incidence of secondary treatments (i.e., reoperations or epidurals) than patients who did not have spinous process fractures, while ZCQ and secondary outcomes were also comparable. This is important to note since the radiographically-detected spinous process fractures documented in this study using highly specialized equipment and monitoring did not directly translate to negative clinical sequelae (e.g., lower pain/function scores, reoperations, epidurals). This, in combination with the fact that most such radiographically-detected spinous process fractures were asymptomatic, suggests that the radiographic observation of fractures were not consequential adverse events in terms of clinical sequelae.

The forthcoming sections first outline the incidence of these observations, characterization of the specific radiographic observations, and correlation to values presented in the literature. Then, analyses of the incidence of these radiographic observations compared with preoperative and immediate post-operative measurements is performed to determine potential risk factors. Finally, the clinical outcomes associated with these radiographic observations are presented.

11.1. Incidence of Spinous Process Fractures

The lumbar spinous process (SP) is a posterior midline bony projection that arises from the junction of the two laminae at each vertebral level to make up the posterior wall of the bony spinal canal. The SP is intended to sustain loading under tension with a primary role to serve as a site for muscle and ligamentous attachments, such as the erector spinae, inferior serratus muscles, and lumbar interspinalis. The dorsal aspect of the SP also serves as a point of attachment for the supraspinous ligament which, when under tension, serves to restrict flexion.

Fractures of the lumbar spinous processes have not been widely reported. While numerous cases of cervicothoracic SP fractures ("clay shoveler's fracture") have been previously described,[37,38,39] much fewer reports have described patients who sustained lumbar SP fracture.[40,41,42] In clinical practice, the primary culprits of reported spinous process fracture include direct trauma to the lower back, extreme muscular exertion, coexisting osteoporotic compression fracture, and placement of an interspinous process spacer.

11.1.1. Reporting Methodologies

In the Superion® IDE, there were 2 distinct mechanisms for reporting of spinous process fractures, independent radiographic review and adverse events reported by the site.

- **Independent Radiographic Review:**
  - The core radiographic laboratory (Medical Metrics) independently reviewed all postoperative radiographs (x-rays) for the presence of spinous process fractures using high resolution imaging techniques and radiologists specifically trained in

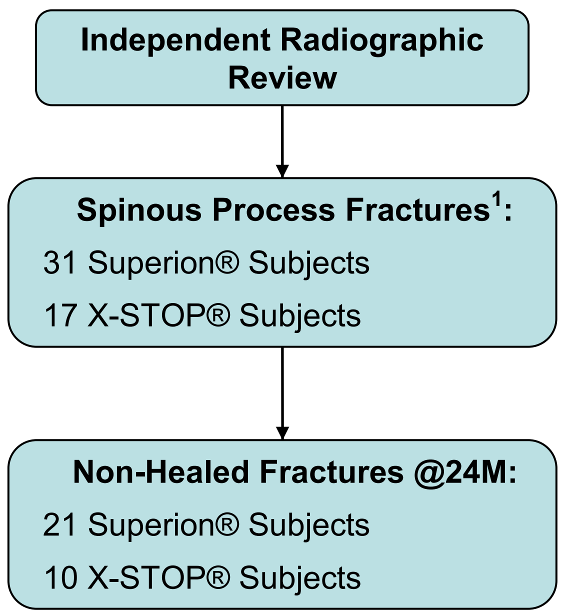
[37] Nuber GW, Schafer MF. Clay shovelers' injuries. A report of two injuries sustained from football. The American journal of sports medicine 1987;15:182-3.
[38] Akhaddar A, El-asri A, Boucetta M. Multiple isolated thoracic spinous process fractures (Clay-Shoveler's fracture). Spine J 2011;11:458-9.
[39] Kang DH, Lee SH. Multiple spinous process fractures of the thoracic vertebrae (Clay-Shoveler's Fracture) in a beginning Golfer: a case report. Spine (Phila Pa 1976) 2009;34:E534-7.
[40] Schroeder JE, Kaplan L, Hasharoni A, Hiller N, Barzilay Y. A hard fall: an isolated fracture of lumbarized S1 spinous process: a case report and review of the literature. Spine (Phila Pa 1976) 2009;34:E864-5.
[41] Jones A, Andrews J, Shoaib A, et al. Avulsion of the L4 spinous process: an unusual injury in a professional rugby player: case report. Spine (Phila Pa 1976) 2005;30:E323-5.
[42] Koehler SM, Lin JD, Stets KC, Qureshi SA, Martins DA, Hecht AC. Lumbar spinous process avulsion fracture in an adolescent dancer. Clinical journal of sport medicine : official journal of the Canadian Academy of Sport Medicine 2010;20:213-4.

the radiographic review of spinous processes and the potential locations of fractures with spinous process devices.

- The radiographic protocol specifically excluded fractures posterior to the implant, such as tip avulsions, due to the lack of potential to affect the mechanism of action of the device, providing a homogeneous assessment of spinous process fractures using a pre-specified definition.
- The time-course of fracture displacement and healing were chronicled as part of the independent review.
- *This assessment was used for the primary endpoint, as specified in the protocol.*

In order to mitigate any reporting bias and standardize the assessment of spinous process fractures, only the results of the independent radiographic review were utilized in the primary endpoint determination.

A description of the incidence of spinous process fractures by these two distinct methods is presented in Figure 10 and Figure 11.



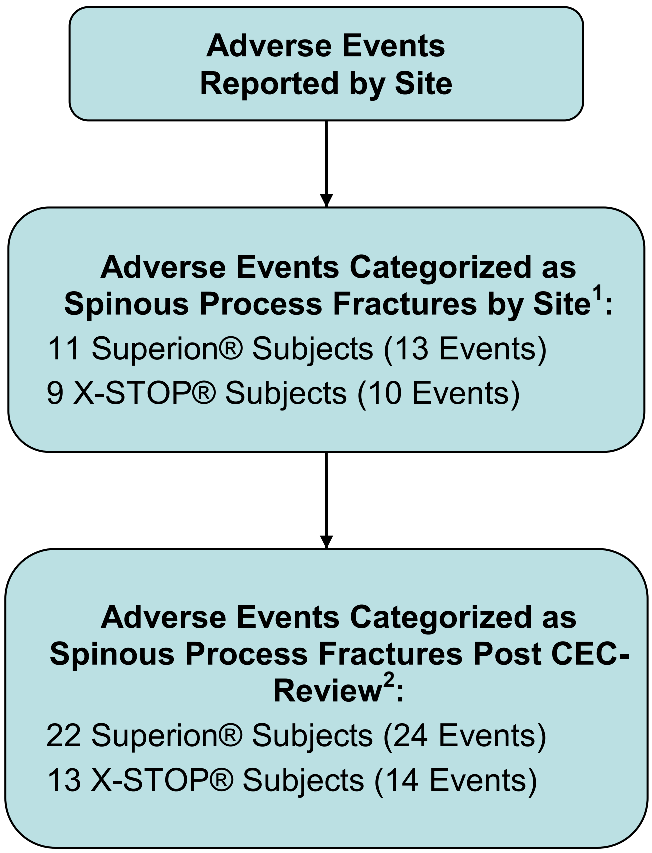
[1]Spinous process fractures reported by the core lab under independent radiographic review followed strict guidelines for reporting.

Figure 10: Incidence of Spinous Process Fractures in Superion® IDE (by Independent Radiographic Review)

Following index surgery through 24 months, 31 of the 190 (16.3%) Superion® mITT subjects had a spinous process fracture identified by the core lab, MMI. In contrast, 17 of the 201 (8.5%) X-STOP® mITT subjects had a spinous process fracture. As stated in the protocol, the definition of spinous process fractures did not include fractures posterior to the implant, such as minor tip avulsions.

- **Adverse Events (Investigator Reported):**

- Study investigators reported spinous process fractures as adverse events. These events were classified by the investigator if they were related to the device or procedure.
- These reported events were based on a variety of observations at the study site level, ranging from perioperative fractures of any portion of the spinous process to fractures observed by radiologists at the clinical sites, providing a heterogeneous assessment based on investigator interpretation.
- As part of the Clinical Events Committee (CEC) review of adverse events (having the results of the independent radiographic review), some events were re-classified as spinous process fractures. This review somewhat standardizes the adverse event reporting, but still retains some heterogeneity of the reporting from the study investigators.
- *This assessment was included in the safety section of the PMA, but not as part of the primary endpoint.*



[1]Spinous process fractures reported by the sites were based on investigator reporting and reported in the "spinous process fracture" category.
[2]Some events reviewed by the CEC were re-classified as spinous process fractures upon review of fracture assessment by MMI as part of the adverse event review. The investigator did not have this information at time of adverse event reporting and categorization.

Figure 11: Incidence of Spinous Process Fractures in Superion® IDE (by Adverse Event Reporting)

As spinous process fractures reported as adverse events did not have strict radiographic criteria associated with the reporting (e.g., inclusion of posterior avulsions), there are adverse events of spinous process fracture not included in the listing of fractures from independent radiographic review by Medical Metrics. In addition, many of the fractures noted by Medical Metrics were not reported as adverse events at the site level due to the high-resolution techniques available at Medical Metrics. This may be attributable to the fact that such fractures were asymptomatic, and as such, went undetected by the clinical investigator.

In order to mitigate any reporting bias and standardize the assessment of spinous process fractures, only the results of the independent radiographic review were utilized in the primary endpoint determination, as described in the protocol for the primary endpoint. This practice is common for Orthopedic and Spine PMAs, given that a radiographic core lab can provide greater sensitivity and consistency to document radiographic events. These investigator reports of spinous process fractures (without confirmation by the independent core laboratory) lack the robust measurements of fracture healing or characterization that fractures reported by the independent core lab have. As the investigator-reported fractures do not have the robustness of the data reporting that is present in the independent radiographic review and are heterogeneous in nature, the adverse events of spinous process fractures from the investigational sites have been included in the safety section rather than in the primary endpoint similar to other spine PMAs including coflex® Interlaminar Technology by Paradigm Spine.

11.1.2. Characterization of Spinous Process Fractures

Spinous process fractures observed via independent radiographic review were further characterized by the timing, location, and fracture displacement. The time course of spinous process fractures in both treatment groups is located in Table 33.

Table 33: Time Course of Spinous Process Fractures in Superion® & X-STOP® Patients

	Post-op	Week 6	Month 3	Month 6	Month 12	Month 18	Month 24	Total
Superion®	4	23	3	-	1	-	-	31
X-STOP®	1	13	2	1	-	-	-	17
Superion®	30/31 (96.7%) btw 0-3 months			1/31 (3.2%) btw 6-24 months				
X-Stop®	16/17 (94.1%) btw 0-3 months			1/17 (5.8%) btw 6-24 months				

As demonstrated in the previous table, the majority of spinous process fractures in both treatment groups are observed within 6 weeks of device implantation. In addition, 4/31 (12.9%) of Superion® patients and 1/17 (5.9%) X-STOP® patients with fractures had an observation of fracture in the immediate post-op x-ray. By 24 months, healed fractures were denoted (as determined by independent radiographic review) in 10 of the 31 Superion® patients (32.3%) and 7 of the 17 X-STOP® patients (41.2%).

A further assessment of the location of spinous process fractures was performed following the initial review. The location of the fracture was categorized as being either in contact with the device or anterior to the device, as depicted in Figure 12.

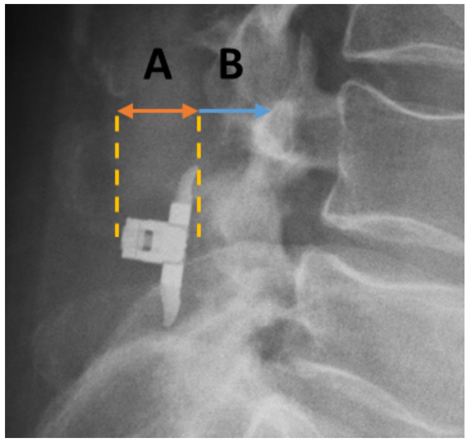


Figure 12: Categorization of Location of Spinous Process Fractures, A: Coincident with Device; B: Anterior to Device

The location of fractures based on this review is presented in Table 34.

Table 34: Location of Spinous Process Fractures in Superion® IDE

Device	Coincident with Device			Anterior to Device		
	n	% of all Fractures	% Healed by 24M	n	% of all Fractures	% Healed by 24M
Superion®[1]	25	80.6%	28.0% (7/25)	4	12.9%	50.0% (2/4)
X-STOP®	5	29.4%	20.0% (1/5)	12	70.6%	50.0% (6/12)

[1]Location of spinous process fracture information was not available for 2 Superion® subjects with fractures.

In the Superion® group, a majority of the fractures (25/31, 80.6%) were present in contact with the device, while in the X-STOP® group, a majority of the fractures (12/17, 70.5%) were present anterior to the placement of the device. Regardless of the device type, the healing rates were similar within each fracture location. Healing was observed at 24 months at a higher rate in fractures that were anterior to the device compared with those fractures coincident with the device.

In addition, an assessment of fracture displacement was also performed by independent radiographic review. A displaced fracture was defined as no contact between the fragment and the remaining vertebra with at least a 2 mm wide gap at some point along the fracture gap. The results from the assessment of fracture displacement are included in Table 35.

Table 35: Displacement of Spinous Process Fractures in Superion® IDE

Device	Displaced Fractures			Non-Displaced Fractures		
	n	% of all Fractures	% Healed by 24M	n	% of all Fractures	% Healed by 24M
Superion®[1]	26	83.9%	23.1% (6/26)	3	9.6%	100.0% (3/3)
X-STOP®	15	88.2%	40.0% (6/15)	2	11.8%	50.0% (1/2)

[1]Displacement of spinous process fracture information was not available for 2 Superion® subjects with fractures.

The majority of fractures in both the Superion® (83.9%) and X-STOP® (88.2%) groups presented as displaced fractures at initial occurrence. However, fracture healing before 24 months was noted in both displaced and non-displaced fractures, although at a higher rate in non-displaced fractures. This is expected since displaced fractures have a larger fracture gap requiring bridging bone to form.

11.1.3. Incidence of Spinous Process Fractures Reported with Similar Devices

Spinous process fractures caused by trauma or degenerative diseases can give insight into the clinical relevance of these fractures. The literature reports that the majority of isolated spinous process fractures can be treated conservatively without lasting sequelae[43].

The reported rate of postoperative spinous process fractures associated with the use of interspinous devices varies greatly, depending on the device implanted and the methodologies used to implant them. In a review of X-STOP® literature, incidence of spinous process fracture was reported in 10 studies, with values ranging from 0% to 29% (pooled incidence: 4.8%, 95% CI: 3.4 to 6.4%). However, none of these studies utilized an independent imaging core laboratory. This literature review is provided in Appendix B.

Kim and co-authors[44] have reported a rather high rate of spinous process fractures in patients receiving X-STOP® (28.9%). However, this study was subject to inherent biases associated with retrospective data collection and review. Furthermore, the sample size in this study is small (38 patients, 50 implants) and at a single site, leading to potential for an inflated rate observed. In addition, the short-term nature of these results (CT at 6 months) does not allow for the determination of healing of the fractures in timing consistent with the results seen in this IDE. Notwithstanding, the studies by Kim showing a higher observance of spinous process fractures using CT imaging demonstrate that review for spinous process fractures can require additional tools for finding these fractures beyond radiologists at a clinical study site. As such, the Superion® study utilized an independent radiographic core laboratory to systematically review all patient radiographs by radiologists specially trained in the detection of spinous process fractures and utilizing both static (neutral) and flexion-extension radiographs.

However, investigation of the results from the Level 1 evidence provided in the coflex® PMA (P110008), a similar incidence of patients with spinous process fractures compared with Superion® patients were observed. As stated in the coflex® SSED:

> "Spinous process fractures were observed by the core radiographic laboratory in 30 coflex® patients (14.0%) and 8 fusion patients (11.9% of patients with spinous processes retained by partial laminectomy). Spinous process fractures were also observed by the investigator surgeons. The incidence of fractures observed by the surgeons differed from

[43] Fayyazi AH, Segal L. Surgical excision of symptomatic lumbar spinous process pseudoarthrosis. J Spinal Disord Tech. 2004 Oct;17(5):439-41.
[44] Kim DH, Tantorski M, Shaw J, Martha J, Li L, Shanti N, Rencu T, Parazin S, Kwon B. Occult spinous process fractures associated with interspinous process spacers. Spine (Phila Pa 1976). 2011 Jul 15;36(16):E1080-5.

that observed by the core radiographic laboratory, as 8 coflex® patients (3.7%) and no fusion patients (0.0%) had spinous process fractures noted by the investigational sites."

The coflex® IDE provides the best comparator for the incidence of spinous process fractures in devices placed in the interspinous space, as an independent radiographic core laboratory was utilized to review radiographs for all patients, and a majority of the fractures reported by independent review were not indicated by the clinical study sites. The determination of spinous process fractures in the fusion group implies that fracture of the spinous processes can occur with and without the placement of devices in the interspinous space.

Peri-operative fractures are not only limited to just spinous process fractures when implanting an interspinous device, but rather, are associated with use of all orthopedic devices. For example, pedicle fractures are known to occur when implanting pedicle screws, with rates ranging from 2-13% of cases in literature specifically looking at this occurrence[45,46,47]. While these rates are lower than the incidence of spinous process fractures observed in the Superion® IDE, they represent a similar type of fracture that occurs during common spinal surgery procedures.

Intra-operative fractures also occur in other orthopedic surgery procedures, notably total hip replacements. In a review of literature specifically evaluating intra-operative fractures[48], intraoperative femoral fracture was encountered during up to 20.9% of revision hip implantations and the rate of periprosthetic fracture during primary total hip arthroplasty was 5.4% when a cementless femoral component was used.

11.1.4. Risk Factors for Spinous Process Fractures in Superion® IDE

An independent radiographic review of all preoperative patient images was performed to determine if a variety of anatomical measurements were correlated with spinous process fractures in both the Superion® and X-STOP® patient cohorts. In addition, baseline patient demographics were reviewed to determine if the incidence of spinous process fractures could be correlated to underlying patient factors.

Demographic Risk Factors

An assessment of underlying demographic factors was performed to determine if these factors had an effect on spinous process fracture incidence. Results with larger magnitude differences in fracture incidence are included in Table 36. Of note, patient sex did not have significant effect on

[45] Suk SI, Kim WJ, Lee SM, Kim JH, Chung ER.Thoracic pedicle screw fixation in spinal deformities: are they really safe? Spine (Phila Pa 1976). 2001 Sep 15;26(18):2049-57.

[46] Esses SI, Sachs BL, Dreyzin V. Complications associated with the technique of pedicle screw fixation. A selected survey of ABS members. Spine (Phila Pa 1976). 1993 Nov;18(15):2231-8.

[47] Di Silvestre M1, Parisini P, Lolli F, Bakaloudis G. Complications of thoracic pedicle screws in scoliosis treatment. Spine (Phila Pa 1976). 2007 Jul 1;32(15):1655-61.

[48] Davidson D, Pike J, Garbuz D, Duncan CP, Masri BA. Intraoperative periprosthetic fractures during total hip arthroplasty. Evaluation and management. J Bone Joint Surg Am. 2008 Sep;90(9):2000-12.

spinous process fracture incidence. Furthermore, patient height and weight were not explored separately, as BMI was deemed to be a better demographic measurement to encompass these measurements. The demographic cut-offs (e.g., age > 67, BMI < 29.5) were selected based on the median value for the respective demographic.

Table 36: Potential Demographic Risk Factors for Spinous Process Fracture

Risk Factor	Superion®			X-STOP®		
	# with Risk Factor	# Fractures	Rate	# with Risk Factor	# Fractures	Rate
Age <67	91	19	20.9%	108	10	9.3%
Age ≥67	99	12	12.1%	93	7	7.5%
BMI < 29.5	104	11	10.6%	102	9	8.8%
BMI ≥ 29.5	86	20	23.3%	99	8	8.1%

In the Superion® cohort, spinous process fracture incidence was increased in patients age <67 and with BMI ≥29.5. The younger patient cohort is more likely to have fewer other health problems than the older cohort, which might suggest that increased patient activity levels immediately following surgery could lead to spinous process fracture, as these events occur primarily in the 3 months following surgery. As a result, labeling revisions are proposed suggesting restriction of patient activity in the 6 weeks following surgery. Patients with BMI ≥29.5 are postulated to be at greater risk for spinous process fracture due to increased loading of the spine. Of particular note, neither of these increased risks led to decreased overall efficacy in the primary endpoint determination for the Superion® device. These are risk factors that can be effectively communicated in the labeling and applied to the patient selection procedure at every institution.

Anatomical Risk Factors

An assessment of underlying radiographic parameters was performed by Medical Metrics to determine if preoperative anatomical differences in patients could be risk factors for spinous process fracture. The anatomical parameters included in this analysis were disc angle, spondylolisthesis, interspinous space height in extension, posterior disc height, and L4 spinous process height and width. The L4 spinous process was isolated for height and width measurements, as it was the predominate location of spinous process fracture in both Superion® and X-STOP® patients.

Based on these assessments, anatomic risk factors associated with spinous process fracture in Superion® patients included higher disc angle, smaller interspinous space height in extension, and L4 spinous process height. For X-STOP®, anatomic risk factors associated with X-STOP® included spondylolisthesis, smaller interspinous space height in extension, and L4 spinous process height. Of note, spondylolisthesis was not correlated with spinous process fractures incidence in Superion® subjects (p>0.6).

Using these identified risk factors as a basis, the relative risk of spinous process fractures was developed based on these identified parameters (Table 37). These rates provide a numerical comparison that gives greater context to risk factors that can be detected radiographically.

Table 37: Potential Preoperative Radiographic Risk Factors for Spinous Process Fracture

Risk Factor	Superion®			X-STOP®		
	# with Risk Factor	# Fractures	Rate	# with Risk Factor	# Fractures	Rate
L4 Spinous Process Height <21mm	58	13	22.4%	53	8	15.1%
L4 Spinous Process Height ≥21mm	115	12	10.4%	125	6	4.8%
Kissing Spinous Processes[1]	49	12	24.4%	60	7	11.7%
Not Kissing Spinous Processes[1]	216	33	15.3%	250	16	6.4%
Grade 1 Spondylolisthesis	69	13	18.8%	78	10	12.8%
No Spondylolisthesis	121	18	14.9%	123	11	8.9%

[1]Defined as levels with a fracture adjacent with <0.2mm separation in extension. Fractures on 2 level patients in the "middle" spinous process are counted twice.

Height of the L4 spinous process and presence of kissing spinous processes were highly linked to incidence of spinous process fracture in both the Superion® and X-STOP® subjects. As a result, VertiFlex® proposes labeling regarding these preoperative radiographic observations, in a similar manner as is presented in the labeling for coflex® Interlaminar Technology. As noted above, no such link is seen with or without spondylolisthesis. While precise measurement of spinous process height on pre-operative radiographs are difficult in a clinical setting, it is common to observe a smaller spinous process. Such an observation, coupled with a precaution in the labeling, would direct the physician to make a more specific height measurement and consider the risk-benefit profile when treating the patient.

Intraoperative Risk Factors

An assessment of device positioning was performed by Medical Metrics to determine if postoperative device positioning could be a risk factor for spinous process fracture. Positioning of the device was assessed on post-op images, with the spinous process divided into 3 sections:

- **Deep** consisting of the anterior 1/3 of the spinous process AP length,
- **Middle** consisting of the middle 1/3 of the spinous process AP length, and
- **Shallow** consisting of the posterior 1/3 of the spinous process AP length.

In addition, the number of levels implanted was assessed to determine if this factor has a relation to spinous process fracture incidence. The results of these assessments are included in Table 38.

Table 38: Potential Intraoperative Risk Factors for Spinous Process Fracture

Risk Factor	Superion®			X-STOP®		
	# with Risk Factor	# Fractures	Rate	# with Risk Factor	# Fractures	Rate
Device Positioning: Shallow[1]	18	8	44.4%	24	6	25.0%
Device Positioning: Middle[1]	220	33	15.0%	189	11	5.8%
Device Positioning: Deep[1]	8	0	0.0%	37	6	16.2%
1 Level Implantation	99	12	12.1%	99	7	7.1%
2 Level Implantation	90	19	19.9%	100	10	10.0%

[1]Fractures on 2 level patients in the "middle" spinous process are counted twice.

The results presented in Table 38 are important for describing device positioning in the surgical technique manual and surgeon training. Device positioning had a significant effect on spinous process fracture incidence in both Superion® and X-STOP® subjects. In particular, shallow positioning of the Superion® device was linked to a 3-fold increase in spinous process fracture incidence over devices placed in the middle of the spinous processes in the anterior-posterior direction. VertiFlex® proposes labeling disclosures and surgeon training to mitigate the risk of spinous process fractures due to shallow device placement. Device placement is an important risk factor since it is directly controlled by the surgeon.

A slightly higher rate of spinous process fractures occurred in Superion® patients with two level implantations. These fractures primarily occurred on the L4 spinous process in a L3/L4 and L4/L5 two level implantation. VertiFlex® proposes labeling to mitigate the risk of spinous process fractures associated with two level implantation.

11.1.5. Summary

The primary driving factor for the increased incidence reporting of spinous process fractures in the Superion® IDE compared with other studies in the literature is the presence of an independent radiographic review by experts trained in the detection of spinous process fractures at all time points, independent of clinical sequelae or other outcome measurements. A similar increase in detection was noted in the coflex® SSED, and that IDE trial utilized the same independent core laboratory for the review of all patients for the presence of spinous process fractures. These fractures were not documented in the X-STOP® IDE since that study did not collect standard radiographs at every timepoint. Radiographs were only collected in response to a clinical presentation of increased pain or loss of function.

From a biomechanical perspective, there are two key differences in the surgical approach for the two devices that contribute to these radiographic events. First, the Superion® device is positioned more closely to the center of rotation of the spine than the X-STOP® device, thus creating different primary loading environments for the two devices. Therefore, if the device is placed properly, the Superion® acts as an extension blocker close to the center of rotation which is an ideal scenario. In this scenario, there is a risk of fracture due to the factors listed above, like smaller/thinner spinous process or kissing spinous processes. Second, the Superion® device is implanted through an MIS approach that does not disrupt adjacent soft tissues and musculature. These same risk factors were seen in other interspinous devices.

However, the X-STOP® is placed more posterior to the center of rotation, which creates a longer moment arm. Since the moment arm is directly proportional to the load and distance from the center of rotation, the greater distance of the X-STOP® implant from the center of rotation results in the implant experiencing a greater moment than the Superion® implant, which in turn requires lower loading of the spine needed to induce injury, and greater risk to migration, and/or dislodgement due to torsional forces (as discussed below). In contrast to the Superion® MIS procedure, the X-STOP is placed through an open approach that disrupts the adjacent and supporting soft tissue and musculature. In addition, since the wings of the X-STOP® are not closely approximated with the spinous processes, the X-STOP® has a greater propensity to migrate or dislodge.

While the incidence of spinous process fractures in the Superion® group is higher than the rates seen in the literature, the use of high resolution imaging and review by expert radiologists at the independent core lab allow for increased detection of these events. Many of the patients who had fractures detected by MMI were ZCQ successes with no back pain adverse events. Furthermore, these fractures occur predominantly within the first 6 months of treatment, indicating a known near-term timing of these events that allows opportunity for proper patient oversight in the weeks immediately following surgery for the mitigation of spinous process fracture. Demographic, radiographic, and intraoperative risk factors were identified leading to increased incidence of spinous process fracture. Using the understanding from these analyses, VertiFlex® proposes labeling disclosures and surgeon training to mitigate these risks associated with spinous process fracture. These labeling and training considerations are designed to allow consistent interpretation across the different types of treatment settings in the United States (e.g., university hospital compared to a smaller rural surgical center). The forthcoming section indicates the clinical sequelae associated with these observations of spinous process fracture.

11.2. Clinical Prognosis for Spinous Process Fractures

11.2.1. Clinical Outcomes from Superion® IDE

Clinical outcomes were correlated with the presence of spinous process fractures identified by independent core lab radiographic review.

Table 39: Clinical Outcome Measurements Stratified by Presence or Absence of Spinous Process Fracture at Any Time Point, 24 Months

24 Month Clinical Outcomes	Superion®		X-STOP®	
	Fracture	No Fracture	Fracture[1]	No Fracture
Pain				
VAS Back: ≥20mm decrease	78.3% (18/23)	64.8% (70/108)	46.2% (6/13)	70.8% (85/120)
VAS Leg (Worse): ≥20mm decrease	73.9% (17/23)	75.9% (82/108)	69.2% (9/13)	78.3% (94/120)
Back & Stenosis-Related Outcomes				
ZCQ Physical Function: ≥0.5 point decrease	73.9% (17/23)	72.2% (78/108)	76.9% (10/13)	80.8% (97/120)
ZCQ Symptom Severity: ≥0.5 point decrease	78.3% (18/23)	76.9% (83/108)	69.2% (9/13)	81.7% (98/120)
ZCQ Patient Satisfaction ≤2.5 points	73.9% (17/23)	86.1% (93/108)	84.6% (11/13)	92.5% (111/120)
ODI: ≥15 point decrease	65.2% (15/23)	63.0% (68/108)	61.5% (8/13)	67.5% (81/120)
Overall Quality of Life				
SF-12 Physical Function: Maintenance or Improvement	77.3% (17/22)	81.1% (86/106)	100.0% (13/13)	88.3% (106/120)
SF-12 Mental Health: Maintenance or Improvement	59.1% (13/22)	60.4% (64/106)	69.2% (9/13)	66.7% (80/120)

[1]Subjects in the fracture group for X-STOP® include those subjects who had an incidence of both spinous process fracture and migration and/or dislodgement.

Overall, the presence of a spinous process fracture did not adversely affect clinical outcomes. Spinous process fracture patients in the Superion® group performed equivalently to Superion® patients with no spinous process fractures. This is best evidenced by the success proportion tables that demonstrate numerically higher success proportions at 24 months.

In contrast, the X-STOP® spinous process fracture patients generally had lower success proportions at 24 months compared to X-STOP® patients with no spinous process fractures. For spinous process fracture patients in the Superion® and X-STOP® groups, the 24 month success proportions for decrease in VAS - Back Pain from preoperative value were 78.3% and 46.2%, respectively. This difference suggests there could be differences in the spinous process fracture outcomes between the two groups that are indicative of differences in design, mechanical interface with the spinous processes, and/or method of action between the two devices. This parallels other discussions that suggest the X-STOP® device has a large surface area that is wedged into the spinous process space. This placement could cause too much distraction that, in turn, causes one of two events: spinous process fracture or migration/dislodgement. In the case of spinous process fracture, VAS – Back Pain results suggest the outcome adversely affects low back pain. These clinical outcomes were not present in the Superion® group, where spinous process fracture patients were more successful in the VAS – Back Pain measurement.

Table 40: Additional Treatments Stratified by Presence or Absence of Spinous Process Fracture at Any Time Point, 24 Months

Treatment Type	Superion®		X-STOP®	
	Fracture	No Fracture	Fracture	No Fracture
Reoperation or Revision	12.9% (4/31)	21.4% (34/159)	11.8% (2/17)	14.5% (27/186)
Epidural Steroid Injection or Nerve Root Block	12.9% (4/31)	13.2% (21/159)	17.6% (3/17)	16.1% (30/186)
Overall Additional Treatment*	**19.4% (6/31)**	**27.7% (44/159)**	**23.5% (4/17)**	**27.4% (51/186)**

*Subjects could have both a reoperation and injection during follow-up.

Additional treatments are important to consider when treating patients presenting in the continuum of stenosis progression. In the Superion® IDE, patients in the Superion® group and X-STOP® group with spinous process fractures had lower re-operation and epidural rates compared to patients with no fracture. These data demonstrate that patients observed to have a spinous process fracture by MMI required an additional treatment at a lower rate than the general population. These results, coupled with the clinical outcomes presented in Table 40, echo the sentiment that many of these fracture patients were asymptomatic and not aware a fracture was present.

By 24 months, healed fractures were denoted (as determined by independent radiographic review) in 10 of the 31 Superion® patients (32.3%) and 7 of the 17 X-STOP® patients (41.2%).

Demonstrable clinical improvement in Superion® subjects having incurred a spinous process fracture suggests that this extension blocking capability is maintained in these subjects, as well. To assess this, the average range of motion (flexion to extension) for the mITT cohort for Superion® subjects with and without spinous process fracture are presented and compared in Table 41, and the changes from pre-op are presented in Table 42, respectively. It is important to note that while spinous process fractures in patients with two-level implants occurred primarily at the spinous process in between implants, a finding of spinous process fracture was "assigned" to all treated levels. As such, the number of levels cited below with a spinous process fracture are higher than the overall number of spinous process fractures.

Table 41: Flexion Extension - Rotation (F to E) (deg) - Superion® mITT Cohort Stratified by Presence or Absence of Spinous Process Fracture

	SPFx						No SPFx								
	At Level(s) of Implant (per level)												t-test	Wilcoxon	Effect
	N	Mean	SD	Med	Min	Max	N	Mean	SD	Med	Min	Max	p-value [1]	p-value [2]	Size [3]
Pre-Op	48	4.39	3.33	3.9	0.0	13.9	224	4.37	3.49	3.6	-9.3	17.0	0.963	0.994	0.01
Month 24	42	3.60	3.57	2.3	0.2	17.3	180	3.26	2.94	2.2	0.0	15.1	0.508	0.603	0.11
Month 36	24	2.43	2.32	2.1	0.0	8.4	113	2.84	2.77	1.6	0.1	11.7	0.494	0.577	-0.15

Table 42: Changes from Pre-Op in Flexion Extension - Rotation (F to E) (deg) - Superion® mITT Cohort Stratified by Presence or Absence of Spinous Process Fracture

	SPFx						No SPFx								
	At Level(s) of Implant (per level)												t-test	Wilcoxon	Effect
	N	Mean	SD	Med	Min	Max	N	Mean	SD	Med	Min	Max	p-value [1]	p-value [2]	Size [3]
Month 24	42	-0.92	3.46	-1.1	-10.1	7.0	177	-1.20	3.36	-0.7	-9.2	7.0	0.628	0.940	0.08
Month 36	24	-1.77	3.10	-0.6	-10.8	2.3	111	-1.67	3.38	-1.0	-9.6	6.8	0.895	0.110	-0.03

The reduction in range of motion from pre-operative measurements is similar for subjects with and without a spinous process fracture at the 24 and 36 month follow up visits. These results indicate that the Superion® device maintains the same extension blocking mechanism of action even with the occurrence of a spinous process fracture.

The average range of motion (flexion to extension) for the mITT cohort for X-STOP® subjects with and without spinous process fracture are presented in Table 43, and the changes from pre-op are presented in Table 44.

Table 43: Flexion Extension - Rotation (F to E) (deg) – X-STOP® mITT Cohort Stratified by Presence or Absence of Spinous Process Fracture

	SPFx						No SPFx								
	At Level(s) of Implant (per level)												t-test	Wilcoxon	Effect
	N	Mean	SD	Med	Min	Max	N	Mean	SD	Med	Min	Max	p-value [1]	p-value [2]	Size [3]
Pre-Op	25	4.04	3.22	3.2	0.4	12.3	263	4.65	3.40	3.8	0.0	18.6	0.386	0.381	-0.18
Month 24	24	4.77	4.76	3.5	0.0	16.8	200	3.69	2.85	2.7	0.1	12.8	0.101	0.685	0.35
Month 36	16	4.81	3.80	3.3	0.8	14.4	118	3.54	2.81	2.7	0.1	14.5	0.105	0.198	0.43

Table 44: Changes from Pre-Op in Flexion Extension - Rotation (F to E) (deg) – X-STOP® mITT Cohort Stratified by Presence or Absence of Spinous Process Fracture

	SPFx						No SPFx								
	At Level(s) of Implant (per level)												t-test	Wilcoxon	Effect
	N	Mean	SD	Med	Min	Max	N	Mean	SD	Med	Min	Max	p-value [1]	p-value [2]	Size [3]
Month 24	24	0.30	4.87	-0.5	-11.5	10.6	198	-1.03	3.03	-0.6	-11.4	7.0	0.057	0.102	0.41
Month 36	16	0.15	3.29	-0.5	-6.1	8.2	116	-1.65	3.28	-1.1	-12.2	9.0	0.041	0.683	0.55

In contrast to the Superion® results, X-STOP® subjects with a spinous process fracture did not, on average, demonstrate a reduction in range of motion from preoperative values at the 24 and 36 month follow up visits comparable to that seen in the non-fracture subjects. These results indicate that, on average, spinous process fracture in X-STOP® subjects did not lead to a maintenance of extension blocking mechanism of the device. Of note, however, 41.1% (7/17) of

X-STOP® subjects with a spinous process fracture also had a device migration and/or dislodgement, compared with 0% (0/31) of Superion® subjects with a spinous process fracture.

11.2.2. Clinical Sequelae of Spinous Process Fractures Reported in Similar Devices

Spinous process fractures caused by trauma or degenerative diseases can give insight into the clinical relevance of these fractures. The literature reports that the majority of isolated spinous process fractures can be treated conservatively without lasting sequelae[49]. If clinical sequelae (such as tenderness) are present, immobilization of the fracture site for 4-6 weeks is standard. Case reports of spinous process fractures related to Baastrup disease[50] and Clay Shoveler's fractures[51,52] show that patients with clinically significant spinous process fractures present with associated pain and tenderness. Fractures with clinical sequelae in the cervical, thoracic, or lumbar spine require observation and can lead to reoperation[53,54].

Regardless of etiology, lumbar spinous process fractures are typically viewed as clinically insignificant. According to the thoracolumbar fracture guidance developed by The AO Spine Classification Group[55], SP fractures are classified as Type A0, which implies an insignificant injury that does not compromise the mechanical integrity of the spinal column. Spine injuries that are categorized as A0 include those resulting in no fracture of the vertebra or clinically insignificant fractures of the spinous or transverse processes. More recent proposals to the AO spine injury classification system have suggested that fractures classified as A0 (including isolated fractures of the spinous processes) do not warrant classification, analogous with a diagnosis of no injury.[56] The AO spine injury classification does not consider fractures related to the placement of interspinous devices. However, these fractures are relatively stable due to the preservation of structural and supporting musculature, tendons, and ligaments, which is made possible by the minimally invasive technique. This is further evidenced by the propensity of the spinous process to heal and provide continued favorable clinical outcomes for subjects with fractures.

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[49] Fayyazi AH, Segal L. Surgical excision of symptomatic lumbar spinous process pseudoarthrosis. J Spinal Disord Tech. 2004 Oct;17(5):439-41.

[50] Pinto PS, Boutin RD, Resnick D. Spinous process fractures associated with Baastrup disease. Clin Imaging. 2004 May-Jun;28(3):219-22.

[51] Kang DH, Lee SH. Multiple spinous process fractures of the thoracic vertebrae (Clay-Shoveler's Fracture) in a beginning Golfer: a case report. Spine (Phila Pa 1976). 2009 Jul 1;34(15):E534-7.

[52] Preutu GM. Diagnosis and therapeutic issues in a case of multiple Clay Shoveler's fractures with associated thoracic wedge compression fractures. Brit J Chiprac. 1999 3(2): 31-5.

[53]Kose KC. Case report: the impact of pseudoarthrosis on clinical outcome in isolated spinous process fractures of six adjacent level thoracic vertebrae. MedGenMed. 2006 Mar 14;8(1):67.

[54] Hirsh LF, Duarte LE, Wolfson EH, Gerhard W. Isolated symptomatic cervical spinous process fracture requiring surgery.Case report. J Neurosurg. 1991 Jul;75(1):131-3.

[55] Vaccaro AR, Oner C, Kepler CK, et al. AOSpine thoracolumbar spine injury classification system: fracture description, neurological status, and key modifiers. Spine (Phila Pa 1976) 2013;38:2028-37.

[56] Reinhold M, Audige L, Schnake KJ, Bellabarba C, Dai LY, Oner FC. AO spine injury classification system: a revision proposal for the thoracic and lumbar spine. Eur Spine J 2013;22:2184-201.

The X-STOP® patients with a spinous process fracture experienced somewhat lower rates of composite clinical success, with only 35.3% achieving composite success (without the fracture component). Of those X-STOP® patients with fractures, however, only 11.8% had outcomes warranting a reoperation or revision to remove the device as a result. In contrast, the composite clinical success results in the Superion® group demonstrated that patients with a spinous process fracture did similar to patients without a spinous process fracture (54.8% vs. 57.2%, respectively, excluding the fracture component of the CCS), indicating that a spinous process fracture has different clinical effects in these two treatments. The lesser clinical impact of the fractures in the Superion® arm is notable, as the majority of fractures detected by the radiographic core lab were undetected by the treating physician, and were asymptomatic.

In addition, Bowers et al. (2010) noted, in a study of complications associated with the X-STOP® device at a single institution, a 23% spinous process fracture rate. Of these patients with spinous process fractures, 85% required revision due to pain.[57] Also, none of the X-STOP® spinous process fractures observed in this study progressed to healing or healed. The results from the Superion® IDE are in contrast to these results, as X-STOP® patients with spinous process fractures predominantly did not require reoperation or revision, as described above, and many were observed to heal by 24 months, although there were increases in pain and stenosis symptoms in X-STOP® patients with fractures.

Results from the coflex® PMA (P110008) provide similar outcomes for patients with spinous process fractures compared with Superion® patients, and similar rates of healing. As stated in the coflex® SSED,

> "Spinous process fractures were observed by the core radiographic laboratory in 30 coflex® patients (14.0%) and 8 fusion patients (11.9% of patients with spinous processes retained by partial laminectomy). Spinous process fractures were also observed by the investigator surgeons. The incidence of fractures observed by the surgeons differed from that observed by the core radiographic laboratory, as 8 coflex® patients (3.7%) and no fusion patients (0.0%) had spinous process fractures noted by the investigational sites. 83% of patients in the coflex® group and 75% of patients in fusion group who had spinous process fractures observed by the radiographic laboratory did not have any associated symptoms at the time the fracture was observed. By month 24, 48% of the coflex® spinous process fractures were resolved. Of the unresolved spinous process fractures, 75% were asymptomatic and resulted in no clinical sequelae or loss of foraminal height during the study. None (0%) of the fusion spinous process fractures were resolved by month 24, and 75% of these patients were asymptomatic."

Spinous process fractures were seen in both the Superion® and X-STOP® cohorts. The rate of spinous process fractures was higher in the Superion® group compared to X-STOP® but was comparable to that presented in the coflex® PMA. In the Superion® group, 21 of the 190 (11.0%) subjects had a spinous process fracture that did not heal by Month 24. In contrast, 10 of the 201 (5.0%) X-STOP® mITT subjects had a spinous process fracture that did not heal by Month 24. Many of these fractures were asymptomatic (72.7% Superion®, 66.6% X-STOP®). Further, most of the Superion® patients (>70%) exhibited significant reduction in both back and

[57]Bowers C, Amini A, Dailey AT, Schmidt MH. Dynamic interspinous process stabilization: review of complications associated with the X-STOP device. Neurosurg Focus. 2010 Jun;28(6):E8.

leg pain scores suggesting that, despite the spinous process fracture, patients were gaining relief from their preoperative claudicatory symptoms. As has also been established, the reoperation or revision rates among patients in both arms sustaining a spinous process fracture was equivalent to, if not lower than, the rates observed in the non-fracture population. As surgeons generally would not revise or remove a device without significant pain or other clinical sequelae, the lower revision rate associated with patients with a spinous process fracture are indicative of the general lack of untoward effects of spinous process fractures.

11.2.3. Proposed Risk Mitigation

Based on the data from the Superion® IDE, the risks of spinous process fractures and associated clinical sequelae can be predominantly mitigated through surgeon training and labeling. In particular, warnings and precautions are proposed that explain to surgeons the underlying risk factors for fracture in order to decrease the incidence of spinous process fracture and allow for proper patient monitoring if a fracture does occur. These risk mitigation methods are designed to be employed by all types of spine surgery centers (e.g., university hospitals, rural surgical centers). Notable examples include:

- Cautioning surgeons against "shallow" placement of the implant (i.e., in the dorsal region of the interspinous process space);
- Cautioning surgeons that "kissing" spinous processes and spinous processes that are unusually thin in cephalad-caudal dimension are at increased risk of fracture;
- Cautioning surgeons to restrict patient activity in the weeks immediately following implantation, especially in obese patients, to reduce risk of fracture from increased loading while bone is remodeling;
- Cautioning surgeons that 2-level procedures have an increased risk of fracture, and to exercise particular care in placement technique and increase post-operative monitoring;
- Cautioning surgeons to exercise care in placement technique, especially when removing osteophytes to permit implant placement, so as not to damage surfaces of the spinous processes that will bear implant loading.

In addition, the proposed post-approval studies plan to follow all patients in the original IDE to 5 years to further determine if any long-term risks are associated with spinous process fractures, as well as a new study to assess the incidence of spinous process fractures in a real conditions of use setting.

11.2.4. Spinous Process Fracture Summary

The majority of spinous process fractures identified in the Superion® IDE trial were observed only by independent radiographic analysts trained to identify such events, and were otherwise undetected by the clinical investigators primarily due to the asymptomatic nature of the spinous process fractures. Of those fractures among Superion® patients that were detected, 72.7% were pain and function successes, compared to 66.6% for X-STOP®, strongly suggesting that these patients gained measurable relief from their lumbar stenosis symptoms despite the radiographically-detected failures. Those spinous process fractures reported as adverse events by the clinical investigators were generally noted as being of mild severity. Importantly, analysis of clinical outcome measurements of patients with spinous process fractures noted no differences between these patients and the remainder of the Superion® cohort without a spinous process fracture. This would suggest that the radiological identification of a spinous process fracture among Superion® patients is a "sub-clinical" observation of little or no clinical consequence in most patients, and having no impact upon effectiveness in relieving spinal stenosis symptoms.

From a biomechanical perspective, both the Superion® and X-STOP® devices are designed to relieve symptoms of spinal stenosis by blocking extension, facilitated by the placement of the device in the interspinous space. In the case of the Superion® device where there is a spinous process fracture, the loading environment of the spine allows the device to settle into position once a patient is ambulated through daily locomotion. The data suggests the presence of a spinous process fracture does not interrupt this process. Therefore, as seen in subjects with spinous process fractures, the device continues to block extension in these patients since many of the fractures do not compromise the biomechanical integrity of the motion segment with the device.

Based upon the data from this and other studies, spinous process fractures are a recognized potential side effect of interspinous devices. The data demonstrate that the effectiveness of the device in addressing lumbar stenosis symptoms is largely unaffected by the fracture, and that these fractures are most often asymptomatic, however, establishing that the risks associated with these radiographic observations are low.

11.3. Comparison of Spinous Process Fractures to Device Migration and Dislodgement

As defined in the IDE protocol, patients with radiographic observations of spinous process fracture, device migration, and device dislodgement at 24 months were determined to be study failures. Of patients in the Superion® clinical study, there were 21 Superion® and 30 X-STOP® patients (11.1% vs. 14.9%, p=0.294) who had a radiographic failure as defined in the primary endpoint at 24 months. For purposes of illustration of the phenomenon, an x-ray of an X-STOP® patient with a complete posterior device dislodgement is shown in Figure 13.

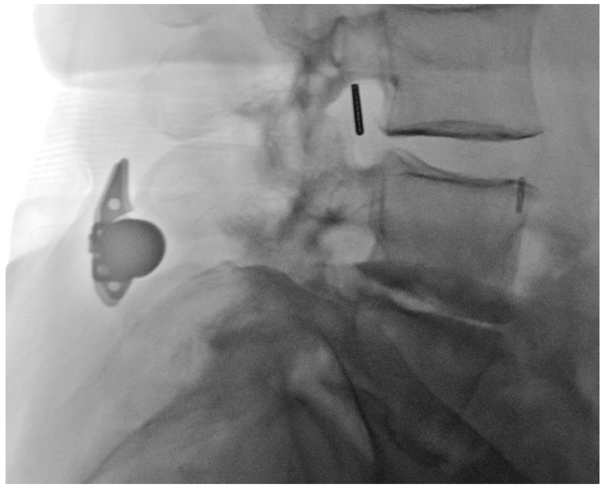

Figure 13: X-ray Depicting Posterior Dislodgement of X-STOP

Migration and dislodgement of X-STOP® devices are known potential complications following X-STOP® surgery, and potential complications associated with such interspinous devices. Unlike spinous process fractures where devices could continue to achieve the mechanism of action, substantial migrations and dislodgements could lead to devices that are unable to physically block extension and perform their mechanism of action. As these events can adversely affect the mechanism of action of the device and can be associated with adverse clinical sequelae, the Superion® IDE included the incidence of significant migration or dislodgement (as measured by independent radiographic review) as part of the primary endpoint for the clinical study.

11.3.1. Incidence of Migration and Dislodgement

In the Superion® IDE, device migration and dislodgement was primarily reported by independent radiographic review by a core laboratory (Medical Metrics, Inc.).

- **Independent Radiographic Review:**
  - The core radiographic laboratory (Medical Metrics) independently reviewed all postoperative radiographs (x-rays) for the presence of migrations or dislodgements using high resolution imaging techniques and radiologists specifically trained in the radiographic review of interspinous devices.
  - The radiographic protocol specifically reports migrations >5mm and dislodgements using specific criteria, providing a homogeneous assessment of migration and dislodgements.
  - The time-course of migration and dislodgement was chronicled as part of the independent review.
  - *This assessment was used for the primary endpoint, as specified in the protocol.*

In order to mitigate any reporting bias and standardize the assessment of device migration and dislodgement, only the results of the independent radiographic review were utilized in the primary endpoint determination.

A description of the incidence of migration, dislodgement, and spinous process fracture in the X-STOP® cohort by independent radiographic review and how the incidences overlap is presented in Figure 14. From this it can be seen that, in many cases, multiple radiographic failure modes were observed in a single patient (e.g., fracture with migration, migration with dislodgement).

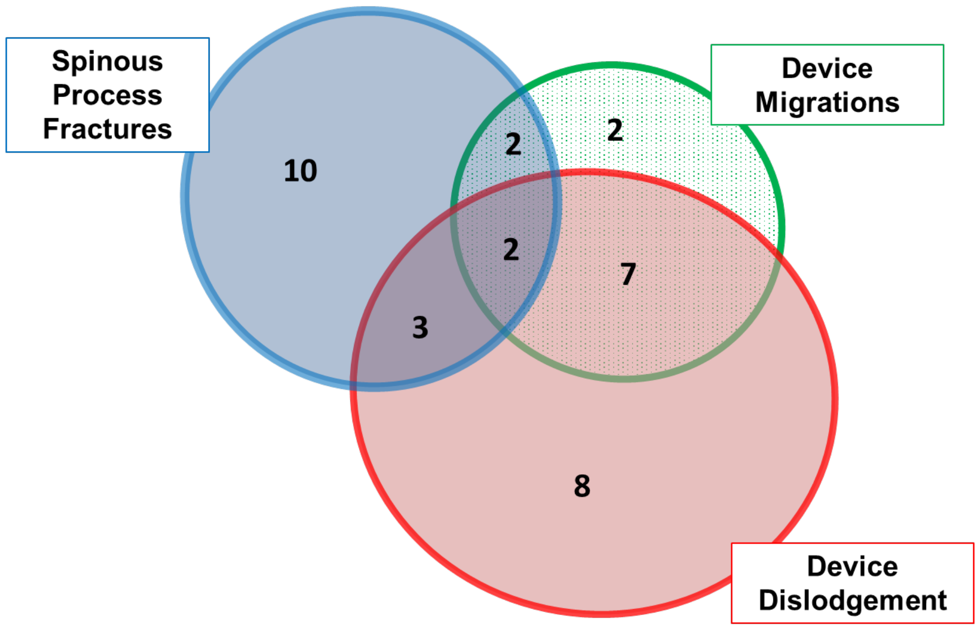

Figure 14: Incidence of Spinous Process Fracture, Device Migration, and Device Dislodgement in the X-STOP® Patient Population. Numbers indicate the number of patients fitting each combination of spinous process fracture, device migration, and device dislodgement.

Overall, 34 X-STOP® subjects had a spinous process fracture, device migration, and/or device dislodgement following index surgery. Of these, 24 of the 201 (11.9%) X-STOP® subjects had a device dislodgement or migration, as reported by independent radiographic assessment. In contrast, none of the Superion® patients exhibited device dislodgement or migration, using the same assessment standards. In contrast to the X-STOP® device, once placed, the Superion® device retained its postoperative position between the spinous processes.

For the patients exhibiting device migration, the maximum amount of migration from post-operative timepoint was quantified in the anterior-posterior direction, as shown in Table 45. The percentage of these patient also exhibiting a spinous process fracture is also shown.

Table 45: Characterization of X-STOP® Device Migration in the Superion® IDE (note: there were no Superion® device migrations documented by Medical Metrics)

Migration Type	X-STOP®		
	n	Mean Maximum Displacement ±SD (mm)	% with Spinous Process Fracture
Migration Only	4	9.3 ± 2.9	50.0% (2/4)
Migration and Dislodgement	9	7.9 ± 3.6	22.2% (2/9)
All Migrations	13	8.4 ± 3.3	30.8% (4/13)

For the patients exhibiting device dislodgement, an assessment was performed to determine the amount of device dislodgement. The results from this assessment are included in Table 46. Here also, the percentage of patients with each type of dislodgement that also sustained a spinous process fracture is also shown.

Table 46: Characterization of Device Dislodgement in the Superion® IDE (note: there were no Superion® device dislodgements documented by Medical Metrics)

Dislodgement Type	X-STOP®			
	n	% of Dislodgements	% with Migration >5mm	% with Spinous Process Fracture
Complete Dislodgement	6	30.0%	33.3% (2/6)	0.0% (0/6)
Superior Dislodgement Only	9	45.0%	44.4% (4/9)	22.2% (2/9)
Inferior Dislodgement Only	5	25.0%	40.0% (3/5)	40.0% (3/5)

11.3.2. Risk Factors for Migrations and Dislodgements

An independent radiographic review of all preoperative patient images was performed to determine if a variety of anatomical measurements were correlated with migrations or dislodgements in the X-STOP® patient cohort. While the X-STOP® is an approved device, it is important to understand the risk factors for all radiographic observations with interspinous devices.

One risk factor for migrations and dislodgements that was explored was the device placement and its potential effects on the spinal biomechanics. In particular, the placement of X-STOP® is commonly more posterior to the center of rotation of the spine compared to Superion®, creating higher axial forces on the device due to normal spinal loading in extension that can lead to device expulsion or migration. Superion®, on the other hand, is generally placed closer to the center of rotation of the spine, which results in a smaller moment arm in extension (i.e., axial load). This, in conjunction with the close approximation of the wings of the Superion® device, may explain the biomechanical theory supporting the absence of Superion® migrations and dislodgements.

In addition to the potential theory above, other risk factors were explored. Baseline patient demographics were reviewed to determine if the incidence of migrations and dislodgements could be correlated to underlying patient factors. A listing of these demographic, radiographic, and intraoperative risk factors are presented in Table 47, Table 48, and Table 49, respectively.

Table 47: Potential Demographic Risk Factors for X-STOP® Migration & Dislodgement

Risk Factor	X-STOP®		
	# with Risk Factor	# Migration/ Dislodgement	Rate
Age <67	108	16	14.8%
Age ≥67	93	8	8.6%
BMI < 29.5	102	7	6.9%
BMI ≥ 29.5	99	17	17.2%

Similar to spinous process fractures in the Superion® group, age <67 and BMI ≥29.5 were associated with greater risks for device migration and dislodgement. These results suggest there are demographic risk factors common to all interspinous devices.

Table 48: Potential Preoperative Radiographic Risk Factors for X-STOP® Migration & Dislodgement

Risk Factor	X-STOP®		
	# with Risk Factor	# Migration/ Dislodgement	Rate
Parallel Spinous Processes	110	9	8.2%
Divergent Spinous Processes	56	6	10.7%
Convergent Spinous Processes	91	6	6.6%
Grade 1 Spondylolisthesis	78	10	12.8%
No Spondylolisthesis	123	14	11.4%

Spinous process shape had a slight effect on the incidence of device migration and dislodgement in the X-STOP® group. In particular, and perhaps not surprisingly, the presence of divergent spinous processes (i.e., those with greater separation dorsally than near the lamina) provided a slight increase in device migration and dislodgement compared to parallel or convergent spinous processes.

Table 49: Potential Intraoperative Risk Factors for X-STOP® Migration & Dislodgement

Risk Factor	X-STOP®		
	# with Risk Factor	# Migration/ Dislodgement	Rate
1 Level Implantation	99	14	14.1%
2 Level Implantation	100	10	10.0%
Device Positioning: Shallow[1]	24	10	41.7%
Device Positioning: Middle[1]	189	9	4.8%
Device Positioning: Deep[1]	37	3	8.1%

[1]Per level of device position. Positioning of the device was assessed on post-op images, with the spinous process divided into 3 sections: “Deep” consisting of the anterior 1/3 of the spinous process AP length, “Middle” consisting of the middle 1/3 of the spinous process AP length, and “Shallow” consisting of the posterior 1/3 of the spinous process AP length.

Postoperative positioning of the X-STOP® device in the posterior “shallow” portion of the interspinous space was linked to a large increase in device migration and dislodgement in X-STOP® subjects. As described above, this location of placement was associated with a much higher incidence of radiographic failures (fractures) in both the Superion® and X-STOP® patient populations. These results suggest there are device placement risk factors common to all interspinous devices. As seen with spinous process fractures, “shallow” device placement contributes to a higher rate of migrations and dislodgements.

11.3.3. Incidence from Other Studies and Literature

Migration and dislodgement in the X-STOP® group is a known risk associated with the use of that device. In a review of X-STOP® literature, incidence of device dislodgement was reported in 8 studies, with values ranging from 0% to 8% (pooled incidence: 5.6%, 95% CI: 4.1 to 7.5%). This literature review is provided as Appendix B. However, none of these studies utilized an independent imaging core laboratory of all patient radiographs and hence, the “true” incidence may have been underreported. Therefore, it was important for the Superion® IDE to thoroughly conduct radiographic observations utilizing an independent core imaging laboratory.

The SSED for X-STOP reported a 1.0% dislodgement rate, although, as noted above, the clinical study supporting that PMA did not perform an extensive radiographic review on all patients or specify collection of radiographic information from all patients. The data presented from the Superion® IDE provides a thorough independent radiographic review to provide an objective assessment of device dislodgements. Furthermore, the corresponding clinical outcome data for these patients allows for the determination of the clinical effects of dislodgements compared with the overall patient population. The results from this study demonstrate that a clear risk of the X-STOP® device is dislodgement that can lead to a decline in overall patient outcomes, while radiographic failures (fractures) associated with the Superion® device do not have this same level of risk. Further, and more importantly, there were no Superion® dislodgements. Device dislodgements can prevent the device from performing its mechanism of action, but further, may be associated with adverse clinical sequelae by requiring later surgical intervention to reposition, replace, or remove the device.

This study was the first randomized, actively controlled study in which the risk of spinous processes fractures, as well as, migrations and dislodgements were fully characterized. While spinous process fractures are a continued risk, given the clinical outcome of the patients that had a spinous process fracture, and the fact that no Superion® device migrated or dislodged, the severity of risk is minimal for the Superion® device. The X-STOP® device not only had a similar risk of spinous process fracture, but also the risk of a possibly clinically significant migration and/or dislodgement.

11.3.4. Clinical Prognosis for Migrations and Dislodgements

Clinical outcomes were correlated with the presence of migrations and dislodgements identified by independent core lab radiographic review, and are presented in Table 50 and Table 51.

Table 50: Clinical Outcome Measurements Stratified by Presence or Absence of Device Migration or Dislodgement at Any Time Point, 24 Months

24 Month Clinical Outcomes	X-STOP®		Superion®
	Dislodgement or Migration	No Dislodgement or Migration	No Dislodgement or Migration
Pain			
VAS Back: ≥20mm decrease	42.1% (8/19)	72.8% (83/114)	67.2% (88/131)
VAS Leg (Worse): ≥20mm decrease	63.2% (12/19)	79.8% (91/114)	75.6% (99/131)
Back & Stenosis-Related Outcomes			
ZCQ Physical Function: ≥0.5 point decrease	78.9% (15/19)	80.7% (92/114)	72.5% (95/131)
ZCQ Symptom Severity: ≥0.5 point decrease	68.4% (13/19)	82.5% (94/114)	77.1% (101/131)
ZCQ Patient Satisfaction ≤2.5 points	89.5% (17/19)	92.1% (105/114)	84.0% (110/131)
ODI: ≥15 point decrease	63.2% (12/19)	67.5% (77/114)	63.4% (83/131)
Overall Quality of Life			
SF-12 Physical Function: Maintenance or Improvement	94.7% (18/19)	88.6% (101/114)	80.5% (103/128)
SF-12 Mental Health: Maintenance or Improvement	63.2% (12/19)	67.5% (77/114)	60.2% (77/128)

Table 51: Additional Treatments Stratified by Presence or Absence of Device Migration or Dislodgement at Any Time Point, 24 Months

Treatment Type	X-STOP®		Superion®
	Dislodgement or Migration	No Dislodgement or Migration	No Dislodgement or Migration
Reoperation or Revision	12.5% (3/24)	14.7% (26/177)	20.0% (38/190)
Epidural Steroid Injection or Nerve Root Block	4.2% (1/24)	18.1% (32/177)	13.2% (25/190)
Overall Additional Treatment*	**19.4% (4/24)**	**28.8% (51/177)**	**26.3% (50/190)**

Similar to the "Overall Additional Treatments" for patients with spinous process fractures, the rates for migration and dislodgement patients were lower than the general population. This further supports the notion that radiographic observations do not necessarily manifest into negative clinical sequelae.

Similar to the review above, two-level X-STOP® subjects with device migration/dislodgement had the observation "assigned" to all treated levels. As such, the number of levels cited below with a device migration or dislodgement is higher than the overall number of subjects with a device migration or dislodgement.

The average range of motion (flexion to extension) for the mITT cohort for X-STOP® subjects with and without device migration/dislodgement are presented in Table 52, and the changes from pre-op are presented in Table 53.

Table 52: Flexion Extension - Rotation (F to E) (deg) – X-STOP® mITT Cohort Stratified by Presence or Absence of Migration/Dislodgement

	Migration/Dislodgement						No Migration/Dislodgement								
	At Level(s) of Implant (per level)												t-test	Wilcoxon	Effect
	N	Mean	SD	Med	Min	Max	N	Mean	SD	Med	Min	Max	p-value [1]	p-value [2]	Size [3]
Pre-Op	32	4.16	3.27	2.9	0.4	12.3	252	4.67	3.41	3.7	0.0	18.6	0.425	0.314	-0.15
Month 24	28	4.81	4.65	3.5	0.0	16.8	196	3.66	2.82	2.8	0.1	12.8	0.061	0.581	0.37
Month 36	16	5.26	4.10	4.5	0.5	14.4	118	3.48	2.72	2.6	0.1	14.5	0.022	0.128	0.61

Table 53: Changes from Pre-Op in Flexion Extension - Rotation (F to E) (deg) – X-STOP® mITT Cohort Stratified by Presence or Absence of Migration/Dislodgement

	Migration/Dislodgement						No Migration/Dislodgement								
	At Level(s) of Implant (per level)												t-test	Wilcoxon	Effect
	N	Mean	SD	Med	Min	Max	N	Mean	SD	Med	Min	Max	p-value [1]	p-value [2]	Size [3]
Month 24	28	0.23	4.76	-0.1	-11.5	10.6	194	-1.05	3.01	-0.7	-11.4	7.0	0.052	0.068	0.39
Month 36	16	0.29	4.41	-0.3	-9.7	9.0	116	-1.67	3.09	-1.1	-12.2	5.4	0.025	0.551	0.60

From these data it is clear that X-STOP® subjects with device migration/dislodgement did not, on average, demonstrate a reduction in range of motion from preoperative values at the 24 and 36 month follow up visits comparable to that seen in the non-migration/dislodgement subjects. These results indicate that, on average, migration/dislodgement in X-STOP® subjects did not lead to a maintenance of extension blocking mechanism of the device.

11.3.5. Migration & Dislodgement Summary

Migration or dislodgement occurred in 11.9% (24/201) of X-STOP® subjects compared to 0.0% (0/191) of Superion® subjects, based on independent radiographic review with strict criteria for detection. These migrations and dislodgements were characterized in order to provide comparable information to that presented for the other radiographic observations in the study, namely spinous process fractures, as 29.2% (7/24) of the migrations and/or spinous process fracture subjects also had a spinous process fracture. The primary risk factor for device migration or dislodgement was shallow device placement postoperatively. From a clinical outcome perspective, X-STOP® subjects with migration and/or dislodgement demonstrated a marked increase in back pain compared to X-STOP® subjects without a migration or dislodgement, as well as higher leg pain and ZCQ symptom severity.

In contrast, there were no observations of migration or dislodgement in the Superion® group based on independent radiographic review. The Superion® device is implanted through an MIS approach that does not disrupt adjacent structural soft tissues and musculature. In that these surrounding tissues are not disturbed, it may be postulated that their natural support contributes to the lack of migrations and dislodgements observed in the Superion® group.

11.3.6. Comparison of Migrations & Dislodgements to Spinous Process Fractures

Understanding the radiographic risks compared to the clinical significance is needed when understanding spinal devices. In particular, the differences in device design led to migrations, dislodgements, and spinous process fractures in the X-STOP® group and only spinous process fractures in the Superion® group. While the incidence of spinous process fractures was higher in the Superion® group, the overall rate of radiographic observations was similar in both treatment groups (16.3% of Superion® vs. 17.9% of X-STOP®, p=0.690).

Table 54: Subjects with Radiographic Observations in the Superion® IDE

Radiographic Observation	Superion® (n=190)		X-STOP® (n=201)	
	n	%	n	%
Spinous Process Fracture (any time)	31	16.3%	17	8.5%
Spinous Process Fracture (non-healed at 24 months)	21	11.1%	10	5.0%
Device Migration (>5mm)	0	0.0%	16	8.0%
Device Dislodgement	0	0.0%	20	10.0%
Any Radiographic Observation (any time)	31	16.3%	34*	16.9%
Any Radiographic Observation (24 months)	21	11.1%	28	13.9%

*Significant overlap was present in X-STOP® subjects having spinous process fractures, device migration, and device dislodgement.

The Superion® IDE utilized an independent core radiographic laboratory (Medical Metrics, Inc.) to review radiographs for evidence of fractures. Medical Metrics has previously performed similar analyses in the coflex® PMA (P110008) as part of the IDE study for this product. In this randomized, prospective study, and through the use of enhanced radiographic techniques, Medical Metrics identified spinous process fractures in 3.75 times more patients than those reported by the sites. Furthermore, Medical Metrics' technology demonstrated the presence of spinous process fractures in patients in the posterolateral fusion cohort who had their spinous processes retained during the laminectomy and fusion procedure, an observation that, to our knowledge, has not been previously reported in the literature. This sensitivity in measurement using plain film radiographs provides for enhanced observation of bony changes in clinical studies of spinal devices, often in patients who have no corresponding symptoms or clinical sequelae.

A similar increase in detection sensitivity of dislodgements and migrations by the core radiographic laboratory is observed in the Superion® clinical study, as well as in others. As the treating clinicians generally detect or observe such events only when adverse clinical manifest and direct the clinician's attention to seeking potential cause, asymptomatic failures of this type may, and did go undetected. Hence, an under-reporting of device dislodgement and migration from individual clinical sites is expected versus rates detected radiographically by an independent core lab.

In both the Superion® and X-STOP® patient populations, spinous process fractures were observed. In addition, to spinous process fractures being seen in both Superion® and X-STOP® patients, migrations and dislodgement were also noted in X-STOP® patients. In many cases, these fractures and device dislodgements/migrations were asymptomatic and had no effect on the patient and their daily life through 24 months. However, in some cases the dislodgements and migrations did demonstrate some clinical significance after the event occurred. Those patients that had an X-STOP® device migrate or dislodge showed an increase in VAS back pain score through 24 months, reflecting increased symptoms, and in many cases had poorer pain and function scores at 24 months compared to those patients in which their device did not migrate or dislodge. This same outcome was not seen in patients that had a spinous process fracture (Table 55), suggesting that adverse clinical sequelae are more commonly associated with device migrations and dislodgements than with fractures.

Table 55: Clinical Outcomes in Superion® IDE Comparing Different Radiographic Observations

24 Month Clinical Outcomes	Superion®	X-STOP®	
	Fracture	Fracture[1]	Dislodgement or Migration
Pain			
VAS Back: ≥20mm decrease	78.3% (18/23)	46.2% (6/13)	42.1% (8/19)
VAS Leg (Worse): ≥20mm decrease	73.9% (17/23)	69.2% (9/13)	63.2% (12/19)

[1]Subjects in the fracture group for X-STOP® include those subjects who had an incidence of both spinous process fracture and migration and/or dislodgement.

In conclusion, the rate of overall radiographic failure, as defined by the *a priori* developed endpoint, was comparable between Superion® and X-STOP® cohorts. As the risk and clinical manifestation of each of the radiographic observations was unknown in the beginning of the study, any evidence of spinous process fracture and/or migration/dislodgement was prospectively considered a study failure, thereby creating an objective method of assessing the safety and effectiveness of Superion® device. In this trial, Superion patients exhibited a statistically significant difference in spinous process fractures, while X-STOP® patients, some of whom also sustained fractures, demonstrated a statistically and clinically significant difference in migrations and dislodgements. While no dislodgements or migrations occurring in the Superion® group, 24 X-STOP® patients had their device migrate and/or dislodge. Although spinous process fractures are associated with recognized risks, given the clinical outcome of the patients that had a spinous process fracture, the severity and impact of such risks is minimal for Superion®. The biomechanics associated with the placement of these interspinous devices, as theorized above, could also play a role in why X-STOP® has a higher likelihood of migrating or dislodging compared to Superion®. However, X-STOP® not only had a risk of spinous process fracture, but also demonstrated the additional risk of a potentially clinically significant device migration and/or dislodgement.

12. CONCLUSIONS

Device Design

The Superion® implant, like the commercially-available control X-STOP® device, is designed to relieve or mitigate symptoms of intermittent neurogenic claudication (primarily leg, buttock, or groin pain and/or weakness), in those individuals who have moderate lumbar spinal stenosis (LSS), and whose symptoms are relieved in flexion. Such symptoms are typically exacerbated when the lumbar spine is in mild extension, as extension serves to further narrow the stenosed nerve channels, thereby compressing the neural elements and triggering or worsening the symptoms. Restricting extension at the symptomatic level(s) is a key objective of these devices.

Placement of the Superion® Interspinous Spacer between two adjacent spinous processes is intended to limit compression of the neural elements at the treated level by blocking extension motion of the affected spinal segment. By preventing or limiting the compression of neural elements in extension, the spacer reduces the symptoms of neurogenic intermittent claudication in patients with moderate spinal stenosis. This principal of "extension blocking" is fundamental to the manner in which interspinous spacers, including both the Superion® device and the control X-STOP® device, achieve their intended effect. This mechanism of action is a function of the size of the implant placed and maintenance of the device's position between the spinous processes.

Both interspinous devices are designed to achieve their mechanisms of action while maintaining the bony structures of the spinal column intact. Further, both devices are placed using techniques that are minimally disruptive of surrounding and supporting tissues, especially the Superion® device. In contrast, a typical direct surgical decompression requires more extensive surgical exposure with its attendant disruption of surrounding soft tissues, and will remove significant amounts of bone from the motion segment in order to relieve pressure and contact on the spinal column and nerve roots. This removal of bone from the motion segment during direct decompression surgery can lead to instability in the spine and potentially cause disc degeneration over time, often requiring further surgical treatment, such as fusion, to treat symptoms associated with the disease.

The minimally invasive nature of both Superion® and X-STOP® provides a conservative surgical option for patients who are unresponsive to non-operative therapies and whose overall health and existing co-morbidities preclude, or put them at increased risk of complications stemming from, a more invasive decompression surgery. Surgeries requiring decompression or decompression with stabilization, such as fusion, carry greater risk for adverse events and have longer recovery times, generally requiring extended hospital and post-surgical care.

Even though the Superion® and X-STOP® devices share similarities, there are clear differences in design and surgical placement techniques. For example, the geometry of the smaller Superion® device is designed to act more as a block between the spinous processes whereas the

X-STOP® device is inserted into place laterally and takes up a larger portion of the interspinous space, which may lead to over-distraction due to an artificial tilt depending on the concavity of the spinous processes. This wedging effect can lead to a short-term improvement in spinal stenosis symptoms, but, based on both the device morphology and more posterior placement of the device, can also lead to spinous process fracture, device migration, and/or device dislodgement. In addition, the "wings" of the Superion® device are designed to closely approximate the spinous processes and retain its position *in situ*, while the "arms" of the X-STOP® device are more widely spaced, do not touch the spinous processes, and may be less effective in maintaining the device's position in the interspinous space.

The surgical technique utilized to implant the Superion® device uses a posterior, minimally invasive approach, wherein the device is inserted through a narrow diameter cannula placed at midline, which requires no surgical dissection of the spinal musculature. Sizing and placement of the device is done through the cannula, with the size measurement performed by an Interspinous Gauge through the cannula. The larger X-STOP® device, by contrast, requires a more invasive surgical procedure for device placement, wherein the skin, fascia, and musculature need be reflected from both sides of the posterior elements to achieve access to the interspinous process space. It may be postulated that this disruption of paraspinal tissues may reduce support for the implant-spinous process "construct." The Superion® IDE clinical trial demonstrated greater perioperative blood loss by patients in the X-STOP® group compared to the Superion® group. It is also notable that, although the rates were very low, post-operative infections requiring irrigation and debridement were higher in the X-STOP® population. Therefore, it is important to consider equivalent clinical outcomes can be achieved through a device with a minimally-invasive procedure.

Clinical Study Design

The Superion® IDE clinical trial was designed to provide evidence that the Superion® device is a safe and effective modality for treating patients who suffer from symptoms of neurogenic intermittent claudication secondary to moderate lumbar spinal stenosis, with or without up to a Grade 1 spondylolisthesis. As with any PMA, a reasonable assurance of safety and effectiveness need be demonstrated through valid scientific evidence. Therefore, the goal of the current IDE study was to demonstrate to the FDA that the Superion® device is safe and effective. In addition, the Superion® IDE was designed to validate the Superion® device's mechanism of action, and demonstrate a reasonable risk-benefit profile of the device compared to the current standard of care. Therefore, a complex and clinically robust composite endpoint was developed, in conjunction with FDA to assess all clinically appropriate safety and effectiveness measurements, as well as, potential risks (i.e., radiographic observations) of the Superion®. For a patient to be an overall study success, he or she had to meet the success criterion for every endpoint regardless of the patient's overall clinical improvement.

The Superion® IDE trial was a prospective, randomized controlled multi-center study. A detailed statistical plan crafted for the study described the *a priori* plan for data analysis for PMA submission. This statistical analysis plan also provided information pertaining to the patient enrollment necessary to achieve statistical non-inferiority in the analysis at the month 24 timepoint.

Study subjects were enrolled to either the investigational group (Superion®) or the control group (X-STOP®) on a randomized basis with the surgeon blinded until after all baseline visit tests were performed and the subject was confirmed to meet all inclusion and exclusion criteria (blinding up until the day of surgery was not possible due to logistical issues with implant kit availability and sterilization) and study subjects were masked from their treatment received. The randomization was a 1:1 investigational:control design. Study subjects were seen and evaluated at timepoints of baseline, post-operative, week 6, month 3, month 6, month 12, month 18 and month 24. The time point for the primary endpoint determination was 24 months; however, clinical data have also been collected annually thereafter, with 36 month data available for approximately two thirds of the overall study population and >90% of those patients theoretically due at 36 months.

The inclusion and exclusion criteria were carefully constructed to ensure enrollment and treatment of the precise patient population who met the proposed Indications for Use for the treatment of moderate spinal stenosis, specifically patients that had failed conservative care and needed surgery to resolve their stenosis symptoms. The nature of their stenosis was measured by their clinical symptoms and radiographic confirmation, which created a homogenous "moderate" stenosis population. In general, the inclusion/exclusion criteria were developed to enroll the most clinically appropriate and homogeneous population by eliminating those exhibiting mild stenosis that were not "sick" enough to warrant an invasive/surgical treatment, as well as those with severe stenosis and other conditions (e.g. >Grade 1 spondy, instability) that would warrant more extensive surgical interventions. In some surgeries, the surgeon had to perform supplemental procedures to clear soft tissue, debulk a facet, or remove an osteophyte, which were performed to allow for proper device placement. The study protocol allowed for these supplemental procedures as long as they did not provide any decompression to the spine.

The complex composite clinical endpoint was designed to provide a complete picture of how the Superion® device performed compared to the X-STOP® device, to establish safety and effectiveness. In this study design, there were four (4) principal components to the primary endpoint, consisting of both effectiveness and safety endpoints. In particular, the Zurich Claudication Questionnaire (ZCQ) was the primary outcome metric used to determine the efficacy of these interspinous devices in treating the symptoms of spinal stenosis. Further, qualitative and quantitative radiographic assessments were also included in the endpoint to identify potential risks to the patient independent of clinical sequelae, and in order to fully understand the comprehensive radiographic and clinical performance profile of the devices, additional clinical and radiographic measurements were gathered. Thirdly, the rate of reoperations and revisions, reflective of failure of the devices to adequately relieve the stenosis symptoms, was considered. Finally, the use of other treatments to address spinal stenosis symptoms (e.g., epidural steroid injections, rhizotomies, spinal cord stimulators) were included as failures. All of these measurements provide a clearer picture of safety and effectiveness of the Superion® device compared to the X-STOP® device. Correlation of the various radiographic measurements with the clinical results also allow for further validation of the mechanism of action of the Superion®.

As stated above, to specifically demonstrate safety of the Superion® device compared to the X-STOP® device, the primary endpoint considered and compared the number of revisions, removals, and re-operations. Since the device is intended to be implanted for the life of the patient, if it has to be removed it could be deemed unsafe or ineffective, and as such, patients requiring revision or reoperation would be considered a study failure. In addition, if the patient experienced a major device related complication, that patient was determined to be a study failure. Also, in an effort to further refine the stringent criteria for study success, any patient who experienced persistent or new symptoms of spinal stenosis that warranted treatment with epidural steroid injection (i.e., where there was symptomatic evidence that the device was not effective in relieving symptoms) was considered a study failure. Lastly, because the device is placed near the spinal canal and could have resulting neurologic sequelae, any worsening motor and/or sensory deficit observed during neurologic assessments would indicate a safety issue and be considered a study failure.

In combination, these clinical and radiographic outcomes metrics served to create a complex primary endpoint that encompassed all relevant measures of safety and effectiveness, and from which a reasonable assessment of risk-to-benefit can be derived.

Clinical Study Results

Study Integrity:

The Superion® IDE regarded study conduct and integrity very seriously and was conducted in line with Good Clinical Practices (GCP), utilizing an independent statistician and Clinical Events Committee (CEC) for data interpretation. For the Superion® IDE, the Superion® cohort had a very robust follow-up rate of 96.7% and the X-STOP® cohort had a follow-up rate of 94.1% through 24 months, providing a very complete dataset from which to base all clinical conclusions and to analyze the composite clinical success. In addition, the use of Bayesian multiple imputation for the primary endpoint allows those patients who were lost to follow up to contribute data to the primary endpoint analysis. Lastly, the excellent follow-up rate and large number of study subjects allows for poolability and sub-analysis of variable clinical populations, including 1- versus 2-level surgery, stenosis, different categories of stenosis, and baseline demographic differences, among others. The data presented in this PMA demonstrate the Superion® device is safe and effective when used in any type of patient at one or two levels. There were no issues of poolability within the covariate analysis, thus creating a full, accountable, and homogenous population to analyze.

In addition, of the subjects who would theoretically be due for their 36 month visit, 90.8% had data available to calculate the primary endpoint at 36 months for supplemental safety and effectiveness data.

Composite Clinical Success:

The composite success measurement was developed to measure the safety and effectiveness of the Superion® device when compared to the X-STOP® device for the treatment of spinal stenosis. This composite success measurement at 24 months includes measurements of clinical efficacy (ZCQ Success), absence of subsequent treatments (epidurals, rhizotomy, spinal cord stimulators), neurological success, and safety (absence of revision or removal) and absence of implant or procedure-related complications (absence of dislodgement, migration, spinous process fracture, or serious device-related adverse events). Non-inferiority of Superion® was established in the primary effectiveness cohort by achieving a Bayesian Posterior Probability > 0.958 (as described in the statistical analysis plan), in the modified Intent-To-Treat (mITT) cohort. The mITT cohort included all patients with an anesthesia start time in the Superion® IDE trial, where 52.7% of Superion® patients and 50.2% X-STOP® patients met the primary endpoint. Further, the demonstration of non-inferiority in the Per Protocol (PP) cohort provides confirmation of the non-inferiority result of the Superion® IDE and demonstrates the robustness of the overall statistical determination, with 53.2% of Superion® subjects and 49.4% of X-STOP subjects meeting the primary endpoint. While the success is just above 50%, the complexity of the endpoint allowed a comprehensive understanding of not only how Superion® performed clinically through ZCQ measurements, but also a thorough characterization of the safety profile and behavior of the device.

Of particular note, at 36 months the composite success (primary endpoint) results demonstrated success in 52.5% of the Superion® subjects and 38.0% of the X-STOP® subjects, establishing that the safety and effectiveness of the Superion® device is durable, being virtually unchanged through that longer term follow-up period.

Effectiveness Analyses:

Based upon the clinical outcome scores, implantation of the Superion® device provides a clear benefit for patients from at least 6 weeks post-operatively (the first post-operative study visit) though 24 months following implantation. Effectiveness, or benefit in reducing or eliminating symptoms of lumbar spinal stenosis, was measured by the primary endpoint and also by a number of secondary outcome metrics. The latter included Oswestry Disability Index (ODI), Visual Analog Scale (VAS for both back pain and leg pain), and the SF-12 quality of life metric. Clinical data from 36 month visits indicate the treatment effect for Superion® is sustained.

The clinical benefits from the Superion® device are seen in a majority of patients, particularly in the relief from stenosis symptoms (as demonstrated by ZCQ symptom severity subdomain) and especially in relief from leg pain (as demonstrated by VAS Leg Pain measurement), which is the predominate expression of neurogenic claudication attributable to lumbar stenosis. The ZCQ physical function domain also improved in these patients, albeit to a lesser degree than the ZCQ symptom severity. While stenosis manifests predominately as buttock, groin, and leg pain, there are patients with associated back pain and related functional limitations. Isolated back pain is often measured by ODI and VAS Back Pain scores. These measurements also demonstrated improvement, albeit to a lesser extent and with a more delayed effect. It should also be noted that the lower rates of clinically significant improvement in these cohorts is indicative of the fact that some patients did not enter the study with a significant amount of back pain and hence could not as easily demonstrate the amount of improvement necessary to meet success criteria in the ODI and/or VAS Back Pain outcomes. Rather, these patients experienced more leg pain and neurogenic claudication as their primary source of lumbar spinal stenosis symptoms. In summary, the effectiveness results at 24 months are comparable to those provided by the X-STOP® device used as the active comparator in this clinical study. Furthermore, as noted above, the clinical outcomes in Superion® patients were maintained at the 36 month visit, establishing the durability of the device's effectiveness.

Safety Evaluations:

The primary safety endpoint was the absence of re-operations, revisions, or supplemental fixation. Through 24 months (as part of the primary endpoint), there were a total of 38 reoperations or revisions in the Superion® group (38/190, 20.0%) compared with 29 reoperations or revision in the X-STOP® group (29/201, 14.4%, p = 0.179). Reoperations and revisions in patients prior to day 730 of treatment were considered to be failures in the primary endpoint. Through the last time point, however, which includes time points past 24 months, there were a total of 49 reoperations or revisions in the Superion® group (49/190, 25.8%) compared with 44 reoperations or revisions in the X-STOP® group (44/201, 21.9%, p = 0.365). The primary reason for reoperation or revision was lack of relief of spinal stenosis symptoms rather than an adverse reaction to or caused by the device or implantation procedure.

In addition to re-operations and revisions, the safety profile of the Superion® device is similar to the X-STOP® device when considering adverse event incidence. In almost every category, the event rate was similar in the Superion® cohort compared to the X-STOP® cohort.

Pain-related adverse events were distributed slightly differently between the Superion® and X-STOP® groups. X-STOP® patients were more likely to have back pain or leg pain adverse events, while Superion® patients were more likely to have buttock or groin adverse events. In addition, X-STOP® patients were more likely to have events related to soft tissue damage or fever. In contrast, Superion® patients were more likely to have an adverse event related to spinous process fracture. The ratio of adverse events of spinous process fractures in Superion® patients to X-STOP® patients is consistent with the results of independent radiographic review, and with other reports of clinical studies of the same or comparable devices. All of these adverse events are indicative of other findings in the study. For instance, X-STOP® had a higher incidence of migration and dislodgement which, as shown in that analysis, had a negative effect on back and leg pain. It was also observed that the X-STOP® surgery is more invasive, which necessarily creates more soft tissue damage compared to that caused by the less invasive (i.e., minimally invasive) Superion® surgery. There were no unusual or unanticipated adverse events in either the Superion® cohort or in the X-STOP® cohort.

Serious adverse events occurred in both arms of the trial at a comparable rate, in 46.3% of Superion® patients compared with 45.8% of X-STOP® patients. In addition, X-STOP® patients exhibited a slightly higher rate of serious adverse events that were device or procedure-related (X-STOP®: 9.5%, Superion®: 8.4%). These device or procedure-related serious adverse events primarily occur the day of surgery through Month 3 postoperatively

Overall, the re-operations and revisions were similar in both groups. Adverse event rates between the Superion® and X-STOP® patients were similar, as well as the types of adverse events. While the different devices each had different associated adverse event rates, the balance of these events, either severe or non-severe, did not tip toward one device or another. Specifically, Superion® patients had more device-related adverse events, compared with X-

STOP® patients, who had more procedure-related adverse events. The data presented in the PMA demonstrates the safety of the Superion® device compared to an approved device (X-STOP®) for the same intended patient population.

Radiographic Analysis

From a clinical perspective, the effects of spinous process fractures, device migration, and device displacement identified by the independent radiographic core lab were reviewed. Following surgery, 16.3% of Superion® and 8.5% X-STOP® mITT subjects exhibited a spinous process fracture, while 11.9% of X-STOP® and 0% of Superion® subjects had a device migration and/or dislodgement.

Several observations from the data are worth noting regarding these radiographic observations. With regard to spinous process fractures, the majority in both arms was detected only by the radiographic core lab, and was not observed by the treating clinician, a common occurrence in orthopedic and spine clinical studies using a radiographic core laboratory. Nor were the fractures themselves symptomatic or otherwise noticed by the patient. Further, the rate of CCS success in Superion® subjects in whom a fracture was detected was comparable to the rate in subjects having no fracture (54.8% vs. 57.2%, respectively, excluding the fracture component of the CCS). The rate of re-operations and removals in the Superion® population having a fracture was also comparable to the rate observed in the entire Superion® randomized cohort (15.1% vs. 21.1%, respectively). Finally, radiographic evidence demonstrates that many of the fractures had healed, or were seen to be healing, by the 24 month visit. These data suggest that the radiographic observations of spinous process fracture did not elicit undue or unexpectedly high rates of adverse clinical sequelae. Further, the secondary outcomes, and specifically those indicative of pain (VAS Back and Leg), were significantly improved in both the overall Superion® cohort, and in the sub-population of Superion® patients sustaining spinous process fractures. For example, 75.6% of patients in the Superion® arm met the success criteria for improvement in VAS Leg Pain (arguably the outcome most reflective of improvement in neurogenic claudication symptoms), *vs*. 73.9% among Superion® patients sustaining a fracture.

Additional analyses identified demographic, radiographic, and intraoperative risk factors leading to increased incidence of spinous process fracture. These factors, such as BMI, spinous process height and shape, and device positioning provide the ability to provide proper labeling designed to significantly reduce the incidence of spinous process fractures. Similar information to mitigate the risk of spinous process fractures is included in the labeling for coflex® Interlaminar Technology.

The data presented from the Superion® IDE also provides a thorough independent radiographic review to provide an objective assessment of device migrations and dislodgements that were reported only in the X-STOP® group. Furthermore, the corresponding clinical outcome data for these patients allows for the determination of the clinical effects of dislodgements compared with the overall patient population. The results from this study demonstrate that a clear risk of the X-STOP® device is migration and/or dislodgement that can lead to a decline in overall patient outcomes, while the Superion® device does not exhibit this same level of risk, as the device is designed to minimize device migration and dislodgement.

Risk/Benefit Profile

The probable benefits associated with use of the Superion® device are primarily based on the data in the clinical study conducted to support PMA approval as described above. The clinical study demonstrated several benefits of the Superion® device over the 24 month time period studied, with additional benefits noted with data through 36 months for the treatment of moderate spinal stenosis. Notably, the study was conducted in a patient population that, while no longer obtaining adequate relief from non-surgical or "conservative" care, did not necessarily present with symptoms and conditions that would require more extensive and invasive surgery. In this population, the device was shown effective in relieving the symptoms of moderate spinal stenosis in the majority of patients treated, notably those of intermittent neurogenic claudication, and the effectiveness is durable through longer term follow-up. Additional information from the clinical literature was utilized to contextualize these benefits in the spectrum of treatments for moderate spinal stenosis, including not only indirect decompression options (X-STOP®), but also direct decompression options such as laminectomy, with or without posterior stabilization.

The Superion® device was statistically non-inferior to X-STOP® in composite clinical success at month 24, constructed as a composite primary endpoint of safety and effectiveness factors. A large percentage of Superion® patients exhibited clinically significant decreases in spinal stenosis symptoms including leg and back pain at 6 weeks to 3 months following surgery, and this treatment effect persisted through 24 months for the primary analysis, and through 36 months with extended follow up, thereby establishing the durability of effect and benefit.

The minimally-invasive nature of the Superion® surgery and smaller overall device size are novel compared to other treatment options, including both indirect and direct decompression options. This minimally-invasive procedure provides lower patient morbidity compared with open procedures like direct surgical decompression, with or without additional stabilization, while offering comparable effectiveness in relieving symptoms. This conservative surgical option offers a benefit to patients whose overall health and existing co-morbidities preclude, or put them at increased risk of complications stemming from a larger decompressive surgery, which would be their only option if not for the use of an interspinous spacer. Surgeries requiring decompression or decompression with fusion also carry greater risk for adverse events and recovery time is significantly longer, generally requiring extended hospital, post-surgical care and return to activities of daily living.

In addition, this minimally invasive surgery and the manner in which the device is implanted requires no alteration to the spinal anatomy, thereby preserving all potential future surgical options in the event that the initial treatment effect is not sustained due to spinal disease progression. As a result, the Superion® device provides a more minimally-invasive option for treating patients with spinal stenosis, adding a novel treatment option for this patient population. In comparison, direct decompression surgery can introduce spinal instability and require more serious interventions, such as spinal fusion, if disease progression occurs or that the initial decompression is ineffective.

The risks associated with the Superion® device are similar in nature to those of the X-STOP® device. The re-operations or revisions seen during the study were primarily due to lack of pain relief and not catastrophic failure of the device. Recognizing the progressive nature of spinal stenosis, these might best be considered “treatment failures” reflective of patients whose disease state has continued to degenerate beyond the ability of the implanted device to have a treatment effect, and not safety-related device failures. Adverse event rates were similar between the two devices. In addition, the risk of having a radiographic observation (spinous process fracture, migration, and dislodgement) was similar between the two devices, although Superion® had more patients with spinous process fractures and X-STOP® had more patients with migrations and dislodgements. Sub-group analyses of these data demonstrate that the radiographic observations in X-STOP® patients were more often linked to clinical sequelae or reduction of device efficacy compared with those Superion® patients with these radiographic observations. Notably, however, the radiographic “observations” of the core lab in the Superion® cohort were typically asymptomatic, were not associated with increases in reoperations or revisions, and were not associated with any lesser effectiveness. The Superion® sub-population in whom the core lab detected a spinous process fracture had equivalent reoperation/revision rates and comparable ZCQ and secondary outcome scores when compared to the Superion® population in which such radiographic failures were not detected. These data, in combination with the fact that these asymptomatic fractures tend to heal over time, suggests that the clinical sequelae of spinous process fractures are minimal. Furthermore, analyses from the clinical data provide methods to mitigate the risks of spinous process fracture through labeling and surgeon training.

Given the available information above, the data support the probable benefits of the Superion® device outweigh the probable risks through two years follow up for the treatment of moderate spinal stenosis, as outlined in the proposed Indications for Use.

Conclusion

The Superion® device demonstrated statistical non-inferiority compared to X-STOP® in a prospective, randomized clinical trial for the treatment of moderate spinal stenosis, presenting valid scientific evidence of the safety and effectiveness of Superion®. The Superion® device was also shown to be effective in relieving the symptoms of neurogenic intermittent claudication, notably extremity pain, in >75% of patients treated. The indications and design of the study were negotiated with FDA prior to initiation of the clinical study and were intended to clearly study the indication of moderate stenosis. This definition of moderate stenosis was established by the X-STOP® PMA and was further refined in the development of the Superion® IDE. The inclusion/exclusion criteria were developed to enroll a homogenous population that exhibited the clinical symptoms and radiographic signs of moderate stenosis. The primary endpoints of the study were designed to assess the safety and effectiveness of the Superion® device by assessing pain and function, safety, and potential risks. In order to truly assess the safety and effectiveness of the Superion® device in a “worst case” manner, VertiFlex and FDA jointly concluded that any confounding findings or potential risks would be counted as study failures. This primary endpoint, albeit complex, allowed a truly critical assessment of the benefit/risk profile of the Superion® device within the primary endpoint. Among these confounding findings were radiographic observations, such as spinous process fractures, or device migrations and dislodgements, as well as other treatments for spinal stenosis symptoms which could “mask” or interfere with evaluation of device effectiveness, such as epidural injections, rhizotomies, and the use of spinal cord stimulators. All radiographic assessments were made by an independent core laboratory expert in the evaluation of spinal radiography. By creating this robust, complex, and objective composite endpoint, VertiFlex was able to generate valid scientific evidence for a determination of safety and effectiveness of the Superion® device at 24 months. To summarize:

- The components of the primary composite endpoint demonstrated similar results between treatment arms in each of the measurements.
- The primary pain and function endpoint, ZCQ, demonstrated similar results through 24 months, and a maintenance of improvement through 36 months for Superion®.
- Secondary outcomes measuring pain (VAS) and function (ODI) established that the Superion® device was highly effective in reducing the symptoms associated with lumbar spinal stenosis.
- The re-operation and revision rate was similar in the Superion® and X-STOP® groups at 24 months, while data through 36 months indicated increasing X-STOP® revisions post-24 months.
- Patients having epidural injections or nerve root blocks at the treated level were considered study failures due to both the need for additional treatment and the confounding effect of the injection on pain measurements. The X-STOP® group had a slightly higher rate of epidural injections compared to Superion®.

Through the results of the clinical study, the Superion® device demonstrated a consistent safety profile, while X-STOP® demonstrated late revisions and lessening of effectiveness beyond 24 months. Re-operations and revisions were primarily due to lack of pain relief, potentially attributable to continued spinal degeneration and/or symptomatology arising from untreated spinal levels. Superion® revisions tended to occur earlier following treatment (<12 months) than did the X-STOP® revisions, which occurred primarily after 12 months of treatment.

The primary difference in the clinical study results between the two devices was the type of radiographically-detected failures, i.e., spinous process fractures, device migrations, and device dislodgements associated with each device. While the overall rate of such failures was comparable in both arms (11.1% Superion®, and 13.9% X-STOP® at 24 months), there were distinct differences in the incidence of each type of failure between devices. All such radiographic observations in the Superion® arm were spinous process fractures, although fractures were also observed in the X-STOP® arm. The rate of spinous process fractures were higher in the Superion® group compared to X-STOP® but not statistically significant. However, there was a statistically higher rate of migration/dislodgement in the X-STOP® group compared to the Superion® group. In fact, there were no device migrations/dislodgements in the Superion® group observed through independent radiographic review, and the spinous process fractures in the X-STOP® group were often associated with device migration or dislodgement, while this phenomenon was not observed in the Superion® group.

As described above, the data demonstrated that there were no clinical sequelae associated with most spinous process fractures and that many of the spinous process fractures healed at 24 months. This was true in both the Superion® and X-STOP® cohorts. However, increased back pain was observed frequently in patients with X-STOP® device migration/dislodgement. From a biomechanical perspective, and extrapolating from the clinical outcomes, the Superion® device continues to block extension following the observation of spinous process fracture, while significant device migration and/or dislodgement from the X-STOP® device can prevent the device from blocking extension and performing its intended mechanism of action.

Despite the lack of demonstrable adverse clinical sequelae associated with spinous process fractures observed in the Superion® population, in order to better train surgeons to mitigate the risk of spinous process fractures, demographic, anatomic, and perioperative factors were investigated. The risk factors for spinous process fracture in Superion® patients include activity level after surgery, BMI, spinous process height, and sub-optimal device placement. VertiFlex believes these are manageable risk factors, and proposes to mitigate these risks using proper labeling and surgeon training to reduce the incidence of spinous process fracture, despite the minimal association with clinical sequelae.

In conclusion, the primary endpoint results demonstrate that the Superion® device performed comparably to the control, and established the statistical non-inferiority determined *a priori* as primary endpoint success. Further, the secondary analyses demonstrate the effectiveness of the Superion® device in the treatment of symptoms secondary to moderate spinal stenosis, and validate the mechanism of action of the device when implanted in this patient population. Adverse event reports from the Superion® IDE establish the safety of the device, demonstrating a comparable safety profile to a currently marketed (and PMA-approved) device for this intended patient population. Radiographically-detected observations occurred at similar rates between device types, and the data demonstrate that the clinical sequelae associated with spinous process fractures in the Superion® arm are not significant, and do not measurably affect outcomes. Because of this, the benefits of Superion® outweigh the risks of the device when used with the proper instructions for use, contraindications, warnings, and precautions. Overall, the data from the Superion® PMA demonstrate the safety and effectiveness of the Superion® supported by valid scientific evidence for the treatment of moderate spinal stenosis.